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Congress Report ESMO 2021

A GLOBAL DIGEST ON APPROACHES IN ADVANCED SOLID TUMORS

Report from the ESMO Congress, 16th – 21st September 2021, virtual congress

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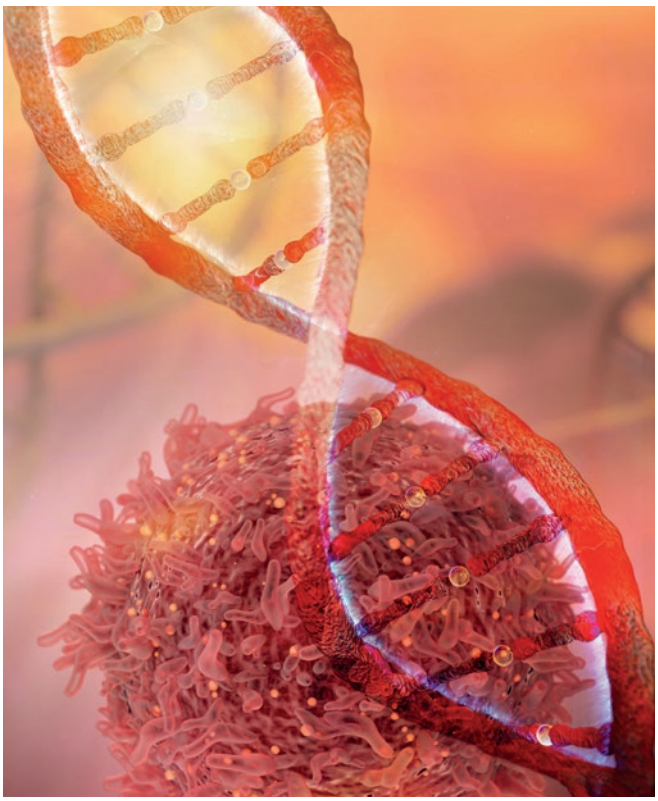

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Preface

Dear Colleagues,

For the second time, the ESMO scientific meeting took place virtually from 16th - 21st September 2021. Despite the challenges of the pandemic, the ESMO committee received an increased number of submitted abstracts compared to last year. Overall, more than 22,700 registrants from 143 countries attended this highly anticipated annual European oncology congress and talks, discussions, and symposia, across 21-track scientific and educational programs, were presented by more than 450 speakers in 170 different sessions.

At this year's meeting, a range of practice-changing new studies were presented, keeping in mind the ESMO's motto of "giving the right treatment at the right time, to the right patient". The very latest standard of care across different solid tumors highlighted the multidisciplinary approach to cancer treatment. Ground-breaking new data presented to the oncology global community aim to allow participants to stay at the cutting edge of research and thus have the potential to change or influence their current clinical practice.

Real-world data that bring an increased added value to prescribers were just some of the highlights of this congress. Additionally, immunotherapy was shown to work across several cancer types, and newcomers in the precision oncology field showed their potential of becoming breakthrough therapies. In colorectal cancer, immune checkpoint inhibitors demonstrated their efficacy and safety, mostly combined with other anti-PD-1 agents and/or with chemotherapy. Moreover, selective and irreversible *KRAS*^{G12C} inhibitors showed promising antitumoral effects by concomitant good tolerance in patients with *KRAS*^{G12C}-mutated CRC, while a new CDK4/6 kinase inhibitor is currently under investigation in therapy-naïve patients with microsatellite stable mCRC. In patients with gastric/gastroesophageal cancer, the 24-month update of the phase III CheckMate 649 study confirmed the benefit of nivolumab plus chemotherapy in this population, while innovative approaches with sintilimab showed encouraging results too. For the treatment of persistent, recurrent, or metastatic cervical cancer, new landmark studies showed an overall survival superiority – regardless of the PD-L1 status at initial diagnosis – for the addition of pembrolizumab to chemotherapy in 1L treatment or for cemiplimab versus chemotherapy after 1L progression. In patients with breast cancer, phase III data with antibody-drug conjugates revealed to be promising in the metastatic setting, while interim data from a new neoadjuvant combination demonstrated antitumoral activity.


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By sharing the latest advances in cancer prevention, diagnosis, and treatment, this second consecutive virtual ESMO 2021 edition perfectly highlighted its tagline: "Connecting and engaging those who care about cancer".

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New horizons in colorectal cancer

FOLFIRINOX: real-world data in first line treatment

Colorectal cancer (CRC) is the second leading cause of cancer death worldwide [1]. About 20 % of CRC patients are diagnosed at the metastatic stage (mCRC), with a 5-year survival rate of 14 % [2]. An AGEO (Association des Gastro-Entérologues Oncologues) multicenter real-world study investigated whether metastases resection rates and survival could be improved when adding a targeted therapy (bevacizumab or anti-EGFR agents) to the triplet-chemotherapy FOLFIRINOX in patients with mCRC; the results were presented at ESMO 2021 [3].

This retrospective study included 332 mCRC patients from 14 centers in France, who started first line treatment between January 2014 and 2019. Among them, 153 patients received FOLFIRINOX (triplet chemotherapy cohort, TC), 146 FOLFIRINOX + bevacizumab (TC-B) and 33 FOLFIRINOX + anti-EGFR (TC-E). Median age was 60.3, 59.5 and 55.1 years in the TC, TC-B and TC-E cohorts, respectively. Between the different cohorts, the primary tumor localization was significantly different ($p = 0.001$), with more rectal cancer in the TC cohort (39.9 %), a majority of right colon tumors in the TC-B cohort (41.1 %) and more left colon tumors in the TC-E cohort (60.6 %).

BRAF mutations were found more frequently in the TC -B group (28.5 %) compared to the TC group (8.6 %) or the TC-E group (3.1 %). RAS mutations were detected in 57.3 % and 55.9 % of the TC and TC-B groups, respectively; as expected, none were found in the TC-E group.

In the TC, TC-B and TC-E cohorts, the median OS reached 34.8, 26.7, and 34.0 months ($p = 0.0841$) and the median PFS

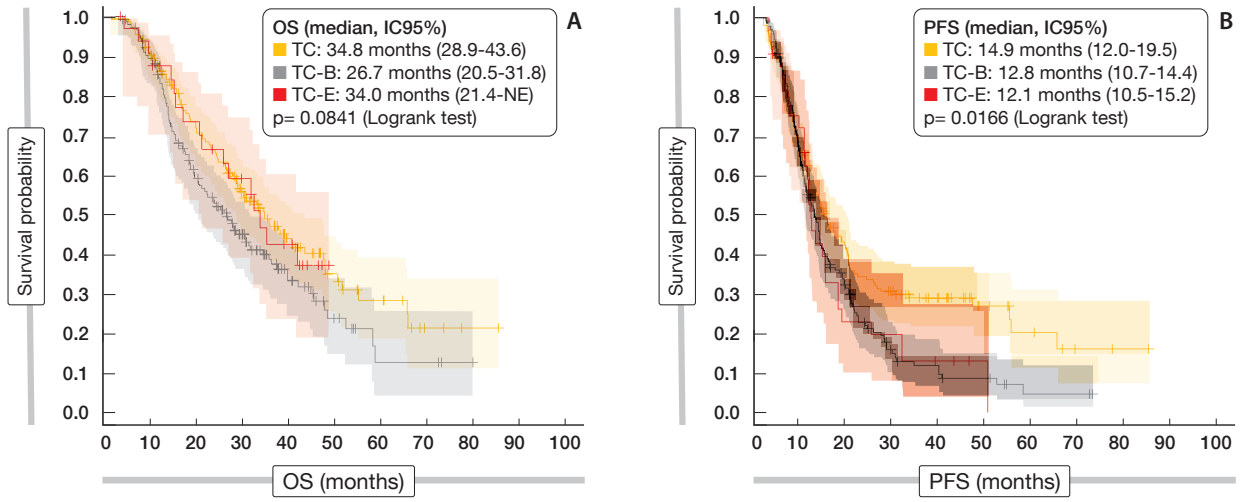

Figure 1: AGEO multicenter real-world study: OS **(A)** and PFS **(B)** according to treatment

14.9, 12.8, and 12.1 months (p = 0.0166), respectively, **(Figure 1)**. After adjusting for age, primitive tumor localization, number of metastasis and primitive tumor resection, overall survival (OS) and progression-free survival (PFS) were similar between the different groups. Metastasis resection rates did not differ significantly between the three investigational groups.

A subgroup analysis of *BRAF*-mutated patients showed a median OS of 17.9 months in the TC cohort and 13.6 months in the TC-B cohort. RAS and BRAF mutations were associated with reduced OS, while no association was observed with PFS.

Grade ≥3 adverse events (AEs) were experienced in 33.3 % (TC cohort), 27.4 % (TC-B cohort) and 34.4 % of patients (TC-E cohort).

In patients with mCRC, a similar efficacy was observed for each treatment analyzed. Considering these results in a real-world population, the authors concluded that further prospective trials are needed to explore the benefit of adding a targeted therapy to the triplet-chemotherapy FOLFIRINOX.

MEDITREME: durvalumab and tremelimumab combined with FOLFOX

Treatment outcomes for patients with advanced CRC remain poor and new therapy options are therefore needed [4]. PD-1/PD-L1 as single immune checkpoint inhibitor (ICI) has not shown any meaningful activity in mCRC patients with microsatellite stable tumors [4]. On the other side, combined blockade with anti-PD1 and CTLA-4 antibodies demonstrated some antitumoral benefit compared with single agent PD-1 inhibitors [4, 5].

At ESMO 2021, Fumet et al. presented results of the single-arm, phase II MEDITREME study, which investigated the efficacy and safety of mFOLFOX6 (6 cycles) in combination with durvalumab (750 mg every 2nd week (Q2W)) and tremelimumab (75 mg/Q4W), followed by durvalumab maintenance therapy in patients with previously untreated *RAS*-mutated mCRC (NCT03202758) [6]. Overall, 57 patients, with a median age of 63.6 years (58 % females), were enrolled. Thirty patients (52 %) had left colon or rectal cancer and 45 patients (79 %) liver metastases. In total, eleven patients (19 %) previously received FOLFOX as adjuvant therapy. Overall, 53 patients (93 %) showed *KRAS* mutations, four patients (7 %) were *NRAS*-mutated and three patients (6 %) presented microsatellite-instability high (MSI-H) tumors.

At one year follow-up, the median PFS reached 8.4 months (95 % CI, 5.9-NR) **(Figure 2A)**; the 6-month PFS rate - the primary endpoint - attained 63.2 % (95 % CI: 49-74), and the 12-month PFS rate was 39.0 % (95 % CI: 26-51). As secondary endpoints, the objective response rate (ORR) reached 61 % and the disease control rate (DCR) was 89 %, including seven complete responses (CR), 29 partial responses

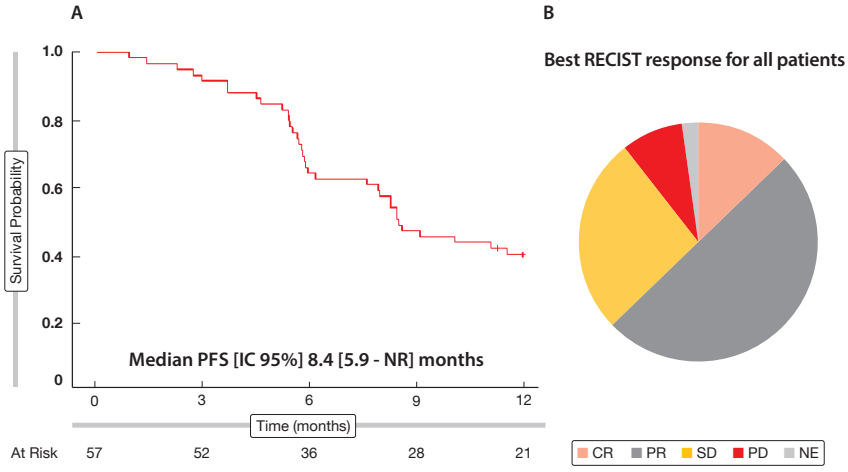

Figure 2: MEDITREME trial: median PFS **(A)** and best response **(B)** according to RECIST v1.1. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

(PR) and 15 stable diseases (SD) **(Figure 2B)**. Translational analyzes showed that high baseline levels of CD4+ helper T cells (Th2) and PD-L1 positive myeloid-derived suppressor cells (MDSC) were associated with poor PFS.

Treatment-related AEs (TRAEs) of grade ≥3 occurred in 75% of patients; the most common grade 3-4 AEs experienced by patients were gastrointestinal and hematological and appear related to chemotherapy as they mainly occurred during the induction period.

Similar PFS rates were observed with this combination compared to other chemotherapy doublet plus target therapies, however, with the major advantage of only three months of chemotherapy. Further analyses are currently being performed to identify which patients might benefit most from this regimen.

Trilaciclib: an innovative first in class CDK4/6 kinase inhibitor

Chemotherapy-induced damage to hematopoietic stem and progenitor cells (HSPCs) results in multi-lineage myelosuppression, which induces neutropenia, anemia and/or thrombocytopenia in treated patients [7]. Trilaciclib, a novel CDK4/6 kinase inhibitor, protects HSPCs and immune cells during chemotherapy exposure (myelopreservation) [8]. On February 12, 2021, the U.S. Food and Drug Administration (FDA) approved trilaciclib as a first in class therapy to reduce the incidence of chemotherapy-induced bone marrow suppression in adults receiving certain types of chemotherapy for extensive-stage small cell lung cancer (SCLC) [8]. Clinical studies in other tumor entities such as breast cancer and colorectal cancer are currently ongoing [8].

PRESERVE 1 is a randomized, phase III study (NCT04607668) evaluating the impact of trilaciclib or placebo on myelopreservation and antitumor activity when administered prior to FOLFOXIRI/bevacizumab in therapy-naïve patients with microsatellite stable (MSS) mCRC [9]. Approximately 296 eligible patients with confirmed unresectable and evaluable disease, ECOG PS ≤1 and adequate organ function are planned to be enrolled in 122 study locations worldwide. Exclusion criteria are prior systemic therapy for mCRC, symptomatic peripheral neuropathy, uncontrolled hypertension, or other contraindications related to FOLFOXIRI/bevacizumab treatment. Patients will be stratified by country, prior therapy, and BRAF V600E mutation status, and randomly assigned 1:1 to receive trilaciclib (240 mg/m^2) or placebo on Day 1 and Day 2 prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to twelve cycles (induction). Following the induction phase, patients will receive trilaciclib or placebo prior to 5FU/leucovorin/bevacizumab therapy. Primary study endpoints are duration of severe neutropenia (SN) in cycle one and occurrence of SN during the induction phase. Secondary endpoints include PFS and OS **(Figure 3)**. The effects of trilaciclib on red blood cell and platelet lineages will also be explored. Recruitment is ongoing.

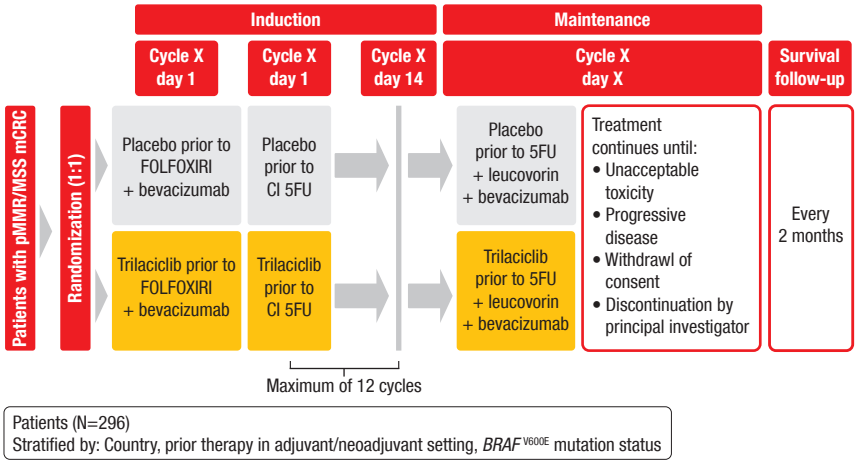

Figure 3: Study design of the phase III PRESERVE 1 trial.

LEAP-017: pembrolizumab plus lenvatinib in 2nd line mCRC

The small subset of mCRC patients with mismatch-repair-deficient (dMMR) and MSI-H derive benefit from immunotherapy, whereas the vast majority of patients with proficient MMR (pMMR) or with microsatellite stable (MSS) CRC do not [10]. The PD-1 inhibitor pembrolizumab was recently approved in Europe as first-line treatment of MSI-H or dMMR mCRC patients [11]. For patients with non-MSI-H or pMMR mCRC, the current first-line standard of care (SOC) is a chemotherapy backbone with or without VEGF and EGFR inhibitors. Thus, the improvement of survival outcomes of those patients and the circumvention of intensive chemotherapy remains an unmet need. In the previously reported phase II LEAP-005 trial (NCT03797326), the combination of pembrolizumab with the multikinase inhibitor (MKI) lenvatinib showed promising antitumor activity with a manageable safety profile [12].

At ESMO 2021, Yoshino et al. presented the study design of the phase III trial LEAP-017 (NCT04776148) evaluating the efficacy and safety of pembrolizumab in combination with lenvatinib compared to investigator's choice of SOC therapy with regorafenib or TAS-102 (trifluridine + tipiracil hydrochloride) in patients with non-MSI-H/dMMR mCRC who have progressed on or after treatment, or have become intolerant to previous therapy [13]. Eligible criteria are the following: ≥18 years; histologically/cytologically confirmed non-MSI-H/dMMR, unresectable or metastatic stage IV (AJCC 8th edition) mCRC; ECOG PS ≤1. Patients will be randomly assigned to pembrolizumab (400 mg intravenously [IV], Q6W) plus lenvatinib (20 mg p.o., once daily) or to regorafenib (160 mg, once daily, Q4W) or TAS-102 (35 mg/m^2, twice daily, Q4W) at investigator's discretion. Stratification will be performed according to the absence/presence of liver metastases. OS constitutes the primary endpoint, while secondary endpoints include PFS, ORR, and DOR per RECIST v1.1 by blinded independent central review, as well as safety and tolerability. Approximately 434 patients will be globally enrolled; the recruitment is currently ongoing at 117 sites in 15 countries or regions worldwide.

Adagrasib combined or not with cetuximab by *KRASG12C* mutation

KRAS is the most frequently mutated oncogene in human cancer and the $KRAS^{G12C}$ mutation occurs in up to 4 % of CRC patients; this oncogenic driver is known to be a strong negative predictive marker of cetuximab efficacy [14]. Adagrasib is a selective and irreversible inhibitor of $KRAS^{G12C}$, whose efficacy has already been demonstrated in non-small cell lung cancer (NSCLC) [15]. During a presentation at ESMO 2021 meeting, J. Weiss hypothesized that the combination of adagrasib and the EGFR inhibitor cetuximab may enhance the inhibition of the *KRAS*-dependent signaling [16].

KRYSTAL-1 was a multi-cohort, phase I/II study (NCT03785249) in patients with unresectable or metastatic solid tumors harboring a $KRAS^{G12C}$ mutation. The recommended dose of 600 mg adagrasib twice daily, which has been set-up in the dose escalation part of the study, was then subsequently evaluated in multiple phase Ib and II expansion cohorts. Primary study endpoints included safety and clinical activity in the phase I, as well as ORR according to RECIST v1.1 in the phase II of the trial.

Preliminary results of adagrasib monotherapy (n = 45) or combination with cetuximab (n = 28) in heavily pretreated $KRAS^{G12C}$-mutated CRC evaluable patients, who had received at least two prior lines of systemic therapies, have been presented at ESMO 2021 [16]. After a median follow-up of nearly nine months, adagrasib monotherapy resulted in an ORR of 22 % and a DCR of 87 % **(Figure 4A)**. Additionally, among the 28 patients evaluable for clinical activity, adagrasib combined with cetuximab led to an ORR of 43 % (including 1 confirmed PR) and a promising DCR of 100 % after a median follow-up of seven months **(Figure 4B)**. At the time of the data cut-off, data for duration of response (DoR) and PFS were still immature in the combination cohort, while 63 % of patients were still on treatment; in the monotherapy arm, median DoR was 4.2 months and median PFS reached 5.6 months.

TRAEs of any grade occurred in all study patients; grade 3-4 TRAEs were experienced by 30 % of patients treated with adagrasib alone and 16 % of patients who received the combined treatment. Those TRAEs led to treatment discontinuation in 6 % in the combination cohort versus none in the monotherapy arm.

Adagrasib showed encouraging antitumoral effects and was well tolerated whether as monotherapy or combined with cetuximab. This combination therapy is currently being evaluated as second-line treatment in the randomized, phase III KRYSTAL-10 study (NCT04793958) of patients with $KRAS^{G12C}$-mutated CRC.

Synergistic effects of sotorasib combined to panitumumab

Sotorasib, a first in class RAS GTPase family inhibitor that selectively and irreversibly targets the $KRAS^{G12C}$ mutation, has shown anticancer activity in solid tumors [17] and was thus FDA approved on May 28, 2021 for patients with $KRAS^{G12C}$-mutated NSCLC [18]. Previous data demonstrated an ORR of 7.1 % in pretreated $KRAS^{G12C}$-mutated CRC patients [17]. As $KRAS^{G12C}$ blockade can lead to accumulation of upstream EGFR signaling, the combination with the anti-EGFR antibody panitumumab might act synergistically

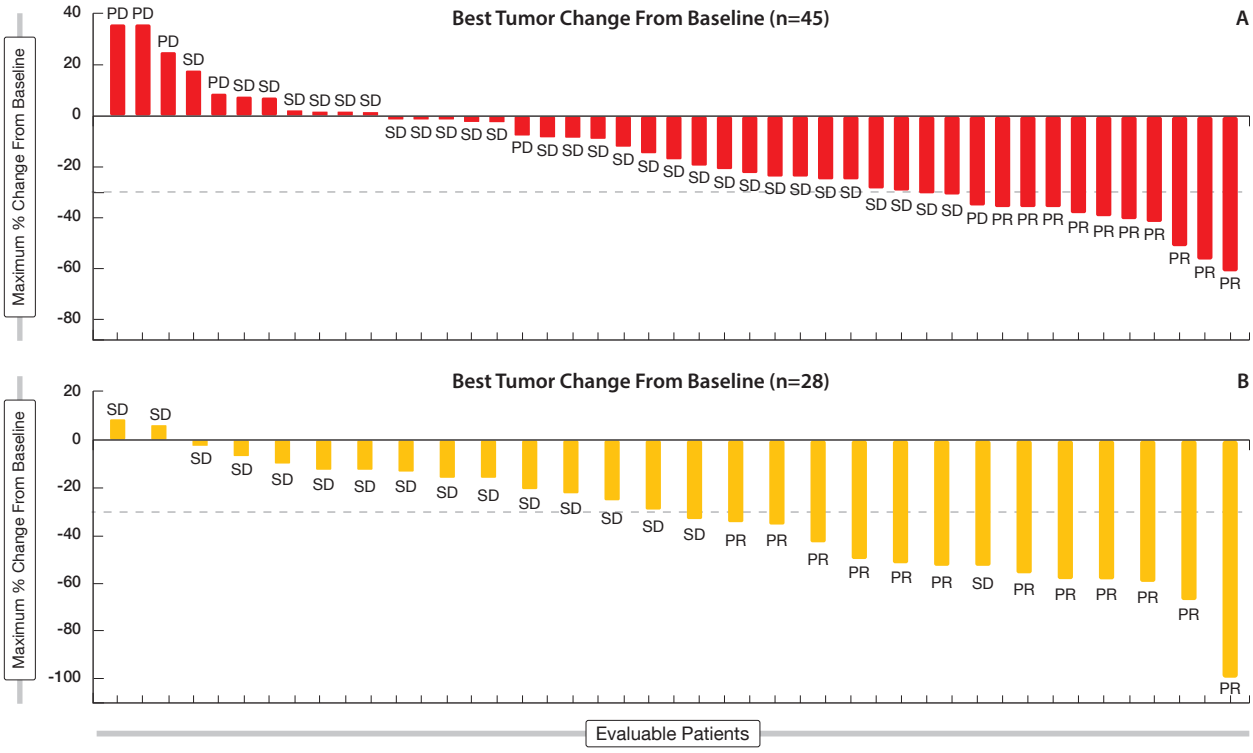

Figure 4: Waterfall plot following adagrasib monotherapy **(A)** and combination **(B)** with cetuximab in the KRYSTAL-1 trial.

to inhibit cancer growth, as suggested by preclinical data [19, 20].

CodeBreaK 101 (NCT04185883) is an ongoing phase Ib study with a dose exploration phase (part 1) to identify a safe and tolerable daily oral dose of sotorasib (960 mg initial p.o. daily, de-escalated to 720 mg or 480 mg) plus panitumumab (6 mg/kg IV, Q2W) in patients with previously treated mCRC, and a dose expansion phase (phase 2) [21]. Cohort A (part 1) comprised patients previously treated with or naïve for $KRAS^{G12C}$ inhibitors whereas Cohort A (part 2) included $KRAS^{G12C}$ naïve patients. Among the 31 patients included so far in Cohort A, median age was 58 years and 67.7 % were female. Five patients (16.1 %) previously received sotorasib and the median treatment duration was 10.3 weeks.

Among eight patients of Cohort A (part 1) (n = 8), DCR was obtained in 75.0 % of patients and ORR was 12.5 %, with one patient achieving a confirmed PR and five having a SD. Tumor shrinkage of 19 to 100 % was detected in two naïve patients and of 15 to 30 % in four previously treated patients. In Cohort A (part 2) (n = 18), DCR was 83.3 % and ORR reached 16.7 %, with three confirmed PRs and twelve SDs. In most patients of Cohort A (part 2), a durable decrease of target lesion size was observed **(Figure 5)**. Overall, patients of the combined Cohort A (n = 26) achieved a DCR of 80.8 % and an ORR of 26.9 %.

No dose-limiting toxicities (DLTs) were observed. A total of 74.2 % of patients experienced TRAEs of any grade (45.2 % related to sotorasib, 74.2 % to panitumumab). Among the 12.9 % of TRAEs grade ≥ 3, dermatitis acneiform (6.5 %), dry skin (3.2 %), diarrhea (3.2 %), hypokalemia (3.2 %), hypomagnesemia (3.2 %) and rash (3.2 %) were the most common ones.

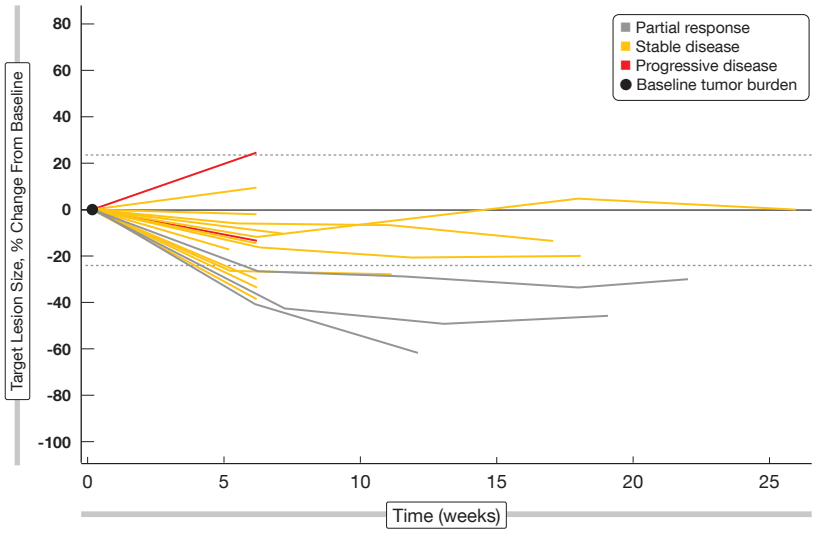

Figure 5: Change in target lesion size of patients in Cohort A (part 2) of the CodeBreaK 101 study.

Considering the results of this early-phase study, the authors concluded that the combination therapy seems to be a safe and tolerable option showing promising efficacy in patients with $KRAS^{G12C}$-mutated CRC.

ALTER-C002: updated results of anlotinib in *RAS/BRAF* wt mCRC

Anlotinib, a novel oral tyrosine kinase inhibitor (TKI) targeting mainly c-kit, PDGF receptor α and β, FGF receptor 1 - 4 and VEGF receptor 2 and 3, exerts an inhibitory effect on tumor growth and angiogenesis. It was first approved as third-line treatment for NSCLC in May 2018, followed by an approval as second-line treatment for advanced soft-tissue sarcoma in June 2019 in China [22].

The open-label, single-arm, phase II study ALTER-C002 (NCT04080843) evaluated the efficacy and safety of anlotinib in combination with capecitabine plus oxaliplatin (CAPEOX) as first-line therapy in patients with *RAS/BRAF* wt mCRC for which preliminary data demonstrated a high antitumor activity and a manageable safety profile [23, 24]. Patients received anlotinib (12 mg p.o., once a day at Day 1-14, Q3W), capecitabine (850 mg/m^2 p.o., twice a day on Day 1-14, Q3W) and oxaliplatin (130 mg/m^2 IV, on Day 1, Q3W) for six cycles, followed by anlotinib plus capecitabine maintenance until disease progression.

Updated results at the data cutoff (April 30, 2021) were presented at ESMO 2021 [25]. Among 30 patients enrolled (median age of 60 years, 13.3 % females, 86.7 % with left colon or rectal cancer, 80 % with liver metastases), 3.3 % achieved a CR, 73.3 % experienced a PR and 16.7 % had a SD **(Figure 6)**. The ORR according to RECIST v1.1, which was defined as the primary endpoint, reached 76.7 %. Secondary outcome measures were DCR (93.3 %) and preliminary median PFS (11.4 months).

Hypertension (46.7 %), decreased neutrophil count (26.7 %) and diarrhea (13.3 %) were the most common TRAEs, while grade 3-4 TRAEs occurred in 76.7 % of patients. No extra bleeding or wound

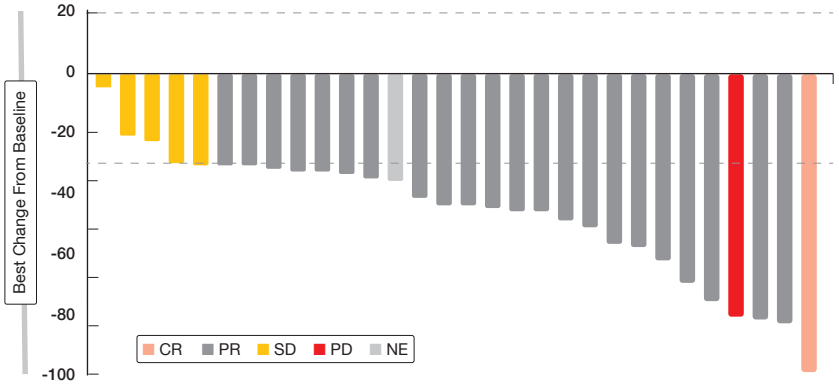

Figure 6: Waterfall plot of patients receiving anlotinib combined with CAPEOX in the ALTER-C002 trial.

healing risk was observed during the perioperative period.

Anlotinib combined with CAPEOX provided a favorable ORR, DCR and PFS in the first-line setting of mCRC and was associated with a manageable safety profile. As a longer follow-up is needed, a phase III study has been recently launched to further assess the efficacy of this combination.

Different dose schedules of cetuximab in *RAS* wild-type mCRC

Cetuximab is indicated for the first-line treatment of patients with EGFR-expressing, *RAS* wild-type (wt) mCRC in combination with FOLFOX; it is administered once a week with an initial dose of 400 mg/m^2, followed by subsequent doses of 250 mg/m^2 [26]. Previous studies showed the noninferiority of the off-label schedule of cetuximab (500 mg/m^2, Q2W) compared with the approved schedule [27-29].

At this year's ESMO meeting, Kasper at al. presented results from a pooled analysis of patient-level data from four studies containing information on tumor locations [30]. Patients were categorized into Q2W or Q1W subgroup based on administration regimen schedule planned at cetuximab initiation. Outcomes were assessed via logistic regression models after inverse probability of treatment weighting (IPTW), using a propensity score considering the same variables as in the main analysis, to account for differences in baseline characteristics between treatment schedules. A total of 830 and 227 patients presented with left- and right-sided primary tumor locations (PTLs), respectively. The overall ORR was 57.5 % (Q1W) and 63.6 % (Q2W), with an odds ratio (OR) of 1.292 (95 % CI: 1.031-1.617); the overall DCR reached 73.6 % (Q1W) and 78.1 % (Q2W), with an OR of 1.278 (95 % CI: 0.987-1.655). The overall resection rate of lung/liver metastases was 15.3 % (Q1W) and 20.4 % (Q2W). In total, serious adverse events (SAEs) occurred in 29.0 % (Q1W) and 30.8 % (Q2W) of patients.

These subgroup analyses depicted no major differences between the two administration schedules (Q1W and Q2W) in terms of ORR, DCR, resection rates, or SAEs in patients with *RAS* wt mCRC with left-and right sided PTLS. ■

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Interview with Prof. Chiara Cremolini, MD, PhD. from Department of Translational Research and New Technologies in Medicine and Surgery University of Pisa, Italy – conducted by Anna Fenzl, PhD.

Colorectal cancer – personalized medicine for a heterogeneous disease

Metastatic colorectal cancer (mCRC), a major cause of death in the Western world, continuous to have a 5-year survival rate below 15 % [1], with microsatellite stable (MSS) mCRC representing the greatest clinical challenge due to its poorly characterized immune microenvironment and immune response [2]. Although the limited response to immunotherapy has led to the assumption that MSS mCRC is immunologically "cold" [2], strategies to make immunotherapy in proficient mismatch repair (pMMR)/MSS mCRC as efficacious as in microsatellite instable (MSI) high/deficient MMR mCRC, are under evaluation [3 - 6]. Which strategies might become available in the future to enhance the efficacy of immunotherapies in the setting of MSS mCRC?

In the Proffered Paper session - Gastrointestinal tumours, colorectal 1, two phase II trials were presented at the ESMO Congress 2021. The introduction of checkpoint inhibitors provided impressive results in MSI mCRC patients, who comprise only 5 % of mCRC patients [6]. Thus, the AtezoTRIBE and MAYA trial, both conducted in Italy, aimed at making immunotherapy an efficacious choice in MSS mCRC, representing the vast majority of mCRC [3, 4].

In the AtezoTRIBE study (NCT03721653) an intensified upfront therapy with FOLFOXIRI plus anti-angiogenic bevacizumab (bev) plus anti-PD-L1 atezolizumab (atezo) was compared to FOLFOXIRI plus bev as first-line treatment of unresectable mCRC patients hypothesizing that the cytotoxic effects of FOLFOXIRI and the immunomodulatory properties of bev may promote the sensitivity to atezo making it an as efficacious treatment approach as in MSS tumors. The primary endpoint was met: the addition of atezo to FOLFOXIRI/bev prolonged the progression free survival (PFS) of mCRC patients resulting in a median PFS of 13.1 months compared with 11.5 months in the control arm (HR 0.69, 80 % CI 0.56-0.85, p=0.012). In the subgroup analysis there was a significant interaction between treatment effect and the MMR status that was determined locally by immunohistochemistry. Although there were only few patients in the deficient MMR subgroup, patients in the experimental arm had not yet reached the mPFS at a median follow up of 20.6 months (HR 0.11, 80 % CI 0.04-0.35, p=0.002). In the proficient MMR subgroup there was still a small efficacious advantage upon treatment with atezo (HR 0.78, 80 % CI 0.62-0.97, p=0.071) [3], although probably less relevant from a clinical point of view.

In the MAYA study (NCT03832621) temozolomide, an alkylating agent, was investigated in a subgroup of mCRC patients with pretreated MSS mCRC and O6-methylguanine-DNA methyl-transferase (MGMT) silencing as centrally assessed by immunohistochemistry + pyrosequencing. These patients received temozolomide as priming agent and upon the achievement of stable disease they were exposed to temozolomide + ipilimumab + nivolumab. The primary endpoint was met with an 8 month PFS rate of 36 % [4]. This interesting strategy deserves further investigation in potentially larger studies.

Given the relevant amount of patients unable to receive multiple lines of treatment as a consequence of rapidly progressive and highly aggressive disease, selecting an appropriate first-line therapy is of highest importance [7]. What can be done to increase the proportion of patients with metastatic colorectal cancer who receive further lines of treatment rather than just one or two?

I would say that the most important thing is choosing the best upfront therapy since we are all aware of the fact that if we have 100 patients starting their first line therapy we will not have 100 patients starting their second or third line and this number decreases step by step [TRIBE2 study, unpublished data]. The more effective the initial therapy is; the more options we can offer these patients for further lines of treatment.

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Indeed, the choice of the first-line therapy is, in my opinion, most relevantly affecting the further lines of treatment of our patients and thus it is the most important choice in the therapeutic route also because in the first-line we have the aim to convert to surgical resectability and thus potentially offer a cure to a subgroup of patients. Summing up, the most important message here is the choice of the first-line therapy accompanied with the active management of the treatment which means to pro-actively manage adverse events and to enable patients to adhere to the treatment plan in order to exploit the most of our therapeutic armamentarium.

Research presented at the ESMO Congress 2021 highlights how the treatment armamentarium is expanding while depicting recent success, unmet needs, and fu ture opportunities in moving toward personalized medicine. What is the optimal continuum of care in 2021 in mCRC in your point of view?

As mentioned previously, I think that choosing the first line therapy is really relevant by a clinical perspective. Today, we have MSI as a molecular marker and major driver for our choices. For MSI tumors, immunotherapy is the standard of care and in my clinical practice this means pembrolizumab [8] while waiting for the results of the combination of the anti-PD-1 antibody

nivolumab plus anti-CTL4-antibody ipilimumab. In the case of MSS tumors we have 2 groups.

Those who are fit and potential candidates for a combination regimen will benefit the most from a chemotherapy doublet plus an anti-EGFR-based treatment in the case of left sided RAS and BRAF wild-type mCRC. Here, we will soon see results from the intensification of the chemotherapy backbone and its effect in molecularly selected patients in combination with anti-EGFR (TRIPLETE study). The triplet plus anti-EGFR is in my opinion not the standard of care yet but has potential to become in the near future once we have understood how relevant the magnitude of benefit is that may be provided by more intensified regimens.

All other patients (right sided and/or *RAS* or *BRAF* mutant) are candidates for chemotherapy + bevacizumab. In BRAF mutant mCRC the added value of FOLFOXIRI has not been confirmed differently than in initial experiences while for others (right-side and/or *RAS* mutant) this is for sure a choice for relatively young patients with an ECOG performance status of 0 and good general condition. On the other hand, for patients that are unfit for a combination, I think the major standard is capecitabine plus bevacizumab [9] but again anti-EGFR may have a place also in combination with 5FU/LV as monotherapy especially in well selected patients with (left-sided) *RAS/BRAF* wild type tumors [10].

Since there is no marker available to predict progressive disease thus avoiding CT scans during maintenance or follow-up after the end of the induction therapy in mCRC you and your colleagues tried to investigate whether the increase of CEA from nadir could predict a progression [11]. Could you highlight the results of the pooled analysis of TRIBE and TRIBE2 studies?

This is an interesting idea that came from one of my collaborators Roberto Moretto. He reflected about the fact that when a patient has completed the induction therapy and has achieved the best response the CT scan at the end of the induction therapy identifies whether he/she is a candidate either for surgery or maintenance. This is a frequent treatment strategy for depotentiating the intensity of chemotherapy while maintaining disease control as longest as possible. In this phase, he asked whether CT scans need to be performed or if CEA level would be enough to predict disease progression. Thanks to the data collected from TRIBE and TRIBE2 study, we found out that having an increase in CEA levels has an accurate predication in terms of disease progression so that we could offer CT scans to patients with a CEA increase more than 10 ng/ml, only, thus sparing patients CT scans every 2 months and still being able to predict disease progression. This means if we detect a high CEA level, a higher CEA level compared to nadir (the lowest value of CEA after baseline), we will ask the patient to perform a CT scan in order to see if a disease progression has occurred and in this is the case we would suggest switching to another line of therapy, otherwise maintenance therapy (or treatment holiday) can be continued. Clearly, in my opinion, these results are not totally practice changing but I think in patients where surgery is no longer a treatment option, we can decide not to go for such a strict monitoring in terms of CT scans but instead use CEA levels, if informative/accurate enough to predict disease progression [11]. ■

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Novel approaches in gastric/gastroesophageal cancer

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer death worldwide [1]. Although gastroesophageal junction (GEJ) cancer, a form of gastric cancer arising in the area of the digestive tract where esophagus and stomach connect, has a lower prevalence than GC, it is continuously rising [1]. Esophageal adenocarcinoma (EAC) joins the list of malignancies as the seventh most common cancer and the sixth leading cause of death from cancer worldwide [1].

CheckMate 649: nivolumab plus chemotherapy

Cytotoxic chemotherapy has remained the standard of care in the first-line therapy of advanced or metastatic HER2-negative GC/GEJC cancer over the past decade but overall survival data are limited to less than one year [2]. Based on CheckMate 649 study results (NCT02872116), the PD-1 inhibitor nivolumab was the first immunotherapy approved by the U.S. Food and Drug Administration (FDA) for the initial treatment of patients with advanced or metastatic GC, GEJ cancer and gastroesophageal adenocarcinoma (GEA) in combination with certain types of chemotherapy [3, 4]. CheckMate 649 randomized naïve patients with advanced/metastatic GC, GEJ cancer and GEJ adenocarcinoma without known HER2-positive status into three arms (NIVO + chemo [nivolumab 360 mg plus XELOX every 3 weeks/Q3W or nivolumab 240 mg plus FOLFOX Q2W], chemo [XELOX Q3W plus FOLFOX Q2W], and NIVO + IPI [nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W for 4 cycles, followed by nivolumab 240 mg Q2W]). This study already showed that the addition of nivolumab led to a superior overall survival (OS), a clinically meaningful progression-free survival (PFS) benefit and a durable response in treatment-naïve patients [4]. A 24-month update of the phase III CheckMate 649 trial was presented at ESMO 2021 [2].

Concerning the dual primary endpoints, among patients, whose tumors expressed PD-L1 at higher levels (PD-L1 CPS ≥5), median OS reached 14.4 months with nivolumab plus chemotherapy versus 11.1 months with chemotherapy alone, while median PFS was 8.1 versus 6.1 months, respectively. nivolumab plus chemotherapy elicited a high objective response rate (ORR) of 60 % compared to 45 % with chemotherapy alone. Thirteen patients in the nivolumab plus chemotherapy arm reached a complete response (CR) and 47 a partial response (PR) versus seven CRs and 38 PRs in the chemotherapy arm **(Figure 1)**. The median duration of response (mDoR) in the investigative and control arms were 9.7 and 7.0 months, respectively. Longer mOS and higher ORR were observed in MSI-H and MSS tumors; however, the magnitude of benefit was greater in MSI-H patients with a mOS of 38.7 months in the nivolumab plus chemotherapy arm versus 12.3 months with chemotherapy alone.

When comparing the nivolumab plus ipilimumab arm with the chemo arm, no significant OS benefit for nivolumab plus ipilumab in the CPS ≥5 group or among all randomized patients was observed. This finding is in contrast to an OS benefit seen with the same combination in the CheckMate 648 study in esophageal squamous cell carcinoma (ESCC) [5]. Although response rates were lower with nivolumab plus ipilumab, this combination therapy did result in a longer duration of response (13.2 versus 6.9 months). Again, patients with high MSI tumors appeared to derive an advantage from the combination therapy.

No new safety signals were identified. For patients who received nivolumab plus chemotherapy, the most common grade 3 to 4 adverse events (AEs) were neutropenia (15 %), decreased neutrophil count (11 %), and anemia (6 %). In the nivolumab plus ipilumab group, patients experienced increased lipase (7 %), increased amylase (4 %) and increased ALT/AST (4% each). With chemotherapy alone, AEs included neutropenia (11-13 %), decreased neutrophil count (9-10 %), and diarrhea (3-4 %). Most immune-related adverse events (irAEs) were grade 1 or 2.

The authors concluded that the longer follow-up data of nivolumab plus chemotherapy further support its use as a new standard first-line treatment in patients with advanced G/GEJ/EA cancer.

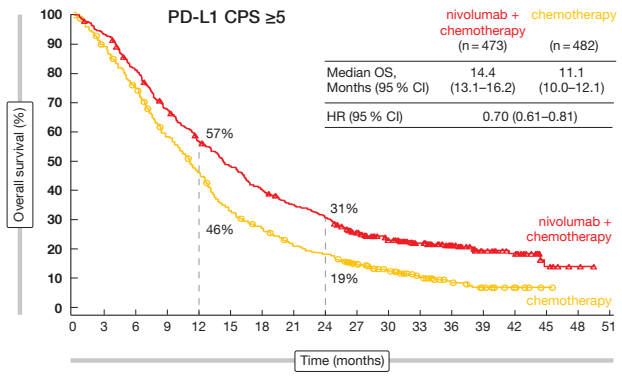

Figure 1: CheckMate 649: overall survival of PD-L1-expressing patients with advanced or metastatic GEA treated with nivolumab plus chemotherapy or chemotherapy alone.

ORIENT-16: OS benefit of novel sintilimab

Sintilimab, a recombinant fully humanized IgG4 monoclonal PD-1 antibody, was first approved in China for the treatment of relapsed or refractory Hodgkin's lymphoma and most recently for the first-line therapy of patients with non-squamous non-small cell lung cancer [6, 7]. As shown in preclinical data, sintilimab has a different binding site than pembrolizumab or nivolumab and showed a potentially greater affinity against PD-1 [8]. Sintilimab is currently under investigation in various solid tumor entities, including esophageal cancer [9]. At ESMO 2021, first results from a prespecified interim analysis of the randomized phase III study ORIENT-16 (NCT03745170) - evaluating sintilimab in combination with chemotherapy compared to chemotherapy alone for the first-

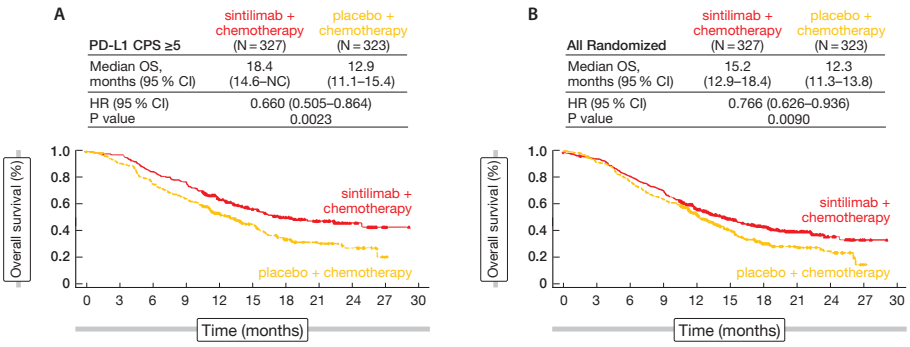

Figure 2: Superior OS benefit with sintilimab plus chemotherapy in PD-L1 CPS ≥5 **(A)** and all randomized patients **(B)**.

line treatment of advanced or metastatic G/GEJ cancer - were presented [10].

As of June 20, 2021, 650 untreated Chinese patients with unresectable locally advanced or metastatic G/GEJ adenocarcinoma, regardless of PD-L1 expression, were randomized 1:1 to receive either sintilimab (3 mg/kg and 200 mg, respectively, for body weights <60 kg and ≥60 kg, IV Q3W) or placebo plus chemotherapy (CapeOX: capecitabine [1000 mg/m^2 oral, twice a day, d1-14, Q3W] for up to 24 months and oxaliplatin [130 mg/m^2 IV, Q3W] up to 6 cycles). Stratification factors were ECOG PS, liver metastases and PD-L1 expression.

The median age of patients was 62 years in the sintilimab plus chemotherapy group compared to 60 years in the placebo plus chemotherapy group. About three quarter were male, most of the patients had GC (81 %), followed by GEJ (18 %), and 91-93 % had a metastatic disease. After a median follow-up of 18.8 months, the dual primary endpoints - OS in patients with a PD-L1 CPS ≥ 5 and in the overall patient population (ITT) - were met. Sintilimab combined with chemotherapy demonstrated superior OS compared to chemotherapy alone, with a 34 % reduction in the risk of death (HR, 0.660; 95 % CI, 0.505-0.864; p = 0.0023) and a 5.5-month improvement in the median OS (18.4 vs. 12.9 months) in patients with CPS ≥ 5; in all randomized patients, a 2.9-month improvement in mOS (15.2 vs. 12.3 months; HR, 0.766; 95 % CI, 0.626-0.936; p = 0.0090) was obtained **(Figure 2)**. The observed OS benefit was consistent in all prespecified subgroup analyses. Similarly, median PFS – the secondary endpoint - was superior in all patients (7.1 vs 5.7 months; HR, 0.636; 95 % CI, 0.525-0.771; p < 0.0001) and those who were PD-L1 CPS ≥ 5 (7.7 vs 5.8 months; HR, 0.628; 95 % CI, 0.489-0.805; p = 0.0002).

In all patients with measurable disease, the ORR was 58.2 % versus 48.4 % in favor of sintilimab, with a median DOR of 9.8 and 7.0 months, respectively. More responders and more durable responses were seen in the sintilimab plus chemotherapy arm.

No additional safety signals were identified for the combination of sintilimab and chemotherapy. Overall, 196 (59.8 %) patients in the experimental arm and 168 (52.5 %) in the chemotherapy arm experienced grade ≥3 treatment-related adverse events (TRAEs). Six (1.8 %) fatal cases in the sintilimab group were related to TRAEs compared with two (0.6 %) in the chemotherapy group. The most common any grade TRAEs (≥ 20 %) across both investigational arms included decreased blood count parameters, anemia, nausea, vomiting, increased AST or ALT, and decreased appetite.

The authors concluded that ORIENT-16 is the first phase III trial in China to demonstrate a significant OS benefit, regardless of PD-L1 expression, and a manageable safety profile with an anti-PD-1 inhibitor combined with chemotherapy in the first-line treatment of advanced GC. The outcomes for lower PD-L1 expression (CPS <1, CPS <5 and CPS <10) were not explicitly presented; however, results shown have demonstrated improvements in patients with higher PD-L1 levels (all patients, CPS >10, CPS >5 and CPS >1), suggesting a lack of improvement in patients with lower PD-L1 levels akin to the CheckMate 649 study and other trials. Thus, data especially in low PD-L1-expressing advanced or metastatic G/GEJ cancer are awaited in the future.

ORIENT-15: superior efficacy of sintilimab in first-line ESCC

ESCC is a histological subtype of esophageal cancer, with distinct incidence and survival patterns among races. Asian patients show a better prognosis in CSM3 mutated ESCC and a higher mutational burden with respect to TP53, EP300, and NFE2L2 [11].

The double-blind phase III ORIENT-15 study (NCT03748134) presented at ESMO 2021 enrolled 659 patients with unresectable locally advanced, recurrent, or metastatic ESCC with a ratio of 1:1 into two arms: either sintilimab (200 mg for ≥ 60 kg, 3 mg/kg for < 60 kg body weight) plus chemotherapy (TP: paclitaxel 175 mg/m^2 plus cisplatin 75 mg/m^2 or CF: cisplatin 75 mg/m^2 plus 5-FU 800 mg/m^2 on day 1-5) or chemotherapy alone [12]. Stratification factors were PD-L1, ECOG PS, liver metastases and chemotherapy.

The median age was approximately 63 years, nearly all patients were Chinese, 86 % were male, and approx. 87 % had a metastatic disease. Most patients in both treatment groups had an ECOG ≤ 1. After a median follow-up of 16 months in the sintilimab plus chemotherapy and 16.9 months in the chemotherapy group, respectively, the median OS - the primary endpoint - significantly favored the experimental arm in all patients at 16.7 versus 12.5 months in the control arm (HR, 0.628; 95 % CI, 0.508-0.777; p < 0.0001). Similarly, in patients with PD-L1 CPS ≥ 10, the median OS favored the combination arm compared to the chemotherapy arm (17.2 versus 13.6 months; HR, 0.638; 95 % CI, 0.480-0.848; p = 0.0018) **(Figure 3)**. Moreover, median PFS was superior in all patients (7.2 vs 5.7 months; HR, 0.558; 95 % CI, 0.461-0.676; p < 0.0001), as well as in those who were PD-L1-positive (8.3 vs 6.4 months; HR, 0.580; 95 % CI, 0.449-0.749; p < 0.0001). The ORR reached 66.1 % for the combined therapy versus 45.5 % in the chemotherapy arm and the median DOR was 9.7 versus 6.9 months, respectively.

Among the patients who received at least one drug dose, TRAE rates were

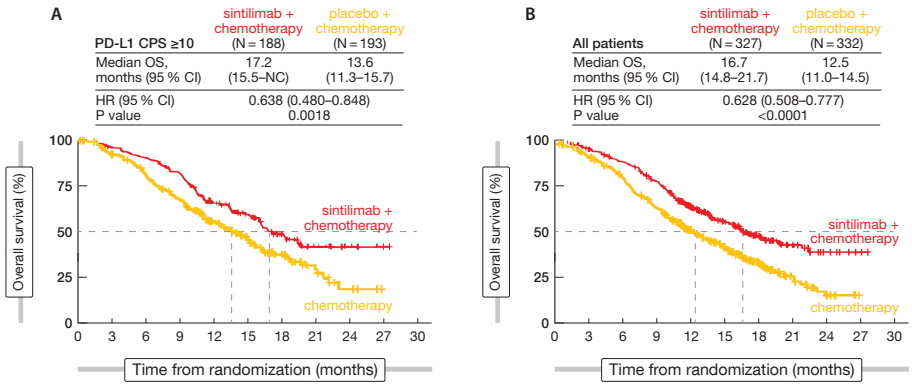

Figure 3: ORIENT-15 trial: Overall survival in PD-L1 high-expressing patients **(A)** and in all patients **(B)**.

98.2 % in both treatment groups. Grade 3 or greater TRAE rates were 59.9 % in the sintilimab plus chemotherapy arm versus 54.5 % in the chemotherapy arm. Discontinuation because of TRAEs resulted in 20.8 % in the combination arm versus 12.3 % in the monotherapy arm, while death rates due to TRAEs were 2.8 % versus 1.8 %, respectively.

Sintilimab in combination with chemotherapy resulted in a significant OS benefit compared to chemotherapy alone in patients with advanced or metastatic ESCC, regardless of PD-L1 expression level, and thus represents a new potential first-line treatment option for this population.

JUPITER-06: toripalimab plus chemotherapy in ESCC

Toripalimab – a novel anti-PD-1 inhibitor – has been previously evaluated in a phase Ib trial in combination with chemotherapy as first-line therapy for the treatment of Asian patients with advanced or metastatic ESCC. The outcome of the randomized, double-blind phase III JUPITER-06 (NCT03829969) was lately presented at the ESMO 2021 meeting [13]. Overall, the JUPITER-06 trial has a very similar design compared to the ORIENT-15 study. PFS by a blinded independent central review per RECIST v1.1 and OS were the co-primary study endpoints.

Among the 514 analyzed patients, the addition of toripalimab to paclitaxel plus cisplatin significantly reduced the risk of death (interim OS analysis: median OS, 17.0 vs 11.0 months; HR, 0.58; 95 % CI, 0.43-0.78; p = 0.00036) and improved PFS (final PFS analysis: 5.7 vs 5.5 months; HR, 0.58; 95 % CI, 0.46-0.74; p < 0.00001) compared with chemotherapy alone.

Overall, 97.3 % of patients experienced any TRAEs in both arms; grade ≥ 3 TRAEs were 64.6 % in the combination arm and 56.0 % in the monotherapy arm. The discontinuation rate because of grade ≥ 3 TRAEs was higher in the toripalimab plus chemotherapy group (2.7 %) compared to the chemotherapy arm (0.4 %); however, fatal AEs were more often with chemotherapy alone (1.2 vs 0.4 %).

JUPITER-06 trial showed the superiority of the combination therapy compared to chemotherapy alone, independently of the PD-L1 expression level, and with an acceptable toxicity. Although the findings from this Asian study are not directly applicable to Caucasian patients, this new treatment combination has the potential to become a new standard first line therapy in patients with advanced or metastatic ESCC.

DisTinGuish: synergistic effect of innovative DKN-01

Since the 1970s, the incidence of GEA has risen considerably in Western countries [14]. Cytotoxic chemotherapy is the standard of care in the first-line therapy; as PD-L1 positivity is common in this type of cancer, immune checkpoint inhibitors (ICIs) are an option in later lines [15]. However, the low response rates and marginal improvements with ICIs in gastric or gastroesophageal junction (G/GEJ) cancers highlight the existing unmet medical need for new and effective treatments, including treatment combinations [15].

A novel approach - currently being investigated in various cancer entities - is DKN-01, a humanized monoclonal antibody that binds to and blocks the activity of Dickkopf-1 (DKK1), a secreted protein modulating the Wnt signaling pathway [16]. DKK1 plays an important antitumoral role in mediating an immuno-suppressive tumor microenvironment since overexpression of DKK1 is associated with a poor clinical prognosis [17]. In September 2020, the FDA granted DKN-01 a fast-track designation for the treatment of patients with DKK1-positive G/GEJ tumors after disease progression.

The combination of DKN-01 with the PD-1 inhibitor pembrolizumab has previously demonstrated anticancer activity in pretreated GEA patients, while high tumoral DKK1 expression was associated with longer PFS [18]. The ongoing phase II trial DisTinGuish (NCT04363801) evaluates the synergy of DKN-01 with the anti-PD-1 antibody tislelizumab in a first- or second line setting with or without chemotherapy in patients with advanced GC or GEJ adenocarcinoma; preliminary data from the first-line cohort were presented at ESMO 2021 [18].

A total of 25 patients were enrolled with a median age of 61 years, 76 % of patients were male, 68 % of them suffered from GEJ adenocarcinoma and 32 % from GC, and 21 patients had tumoral DKK1 mRNA expression available, of whom 57 % were DKK1-high (8 GEJ, 4 GC) and 43 % DKK1-low (7 GEJ, 2 GC). After a median follow-up of five months, the ORR - the primary endpoint - reached 68 % including 15 PR and six SD, while the disease control rate (DCR) was 96 %. Patients whose tumors were DKK1-high showed the highest response rates (DKK-1 high, ORR 90 % versus DKK-1 low, ORR 56 %), and responses were independent of PD-L1 expression **(Figure 4)**. PFS and DoR data were not mature yet and expected in the first half of 2022.

The DisTinGuish trial showed a manageable safety profile; DKN-01-related TRAEs occurred in 56 % of patients with fatigue being the most common one (32 %). Five patients out of 25 individuals in the overall population experienced DKN-01-related TRAEs grade ≥3: pulmonary embolism (2), diarrhea (1), decreased neutrophil count (1), and decreased blood phosphorus (1). Two patients had serious AEs related to DKN-01, one patient

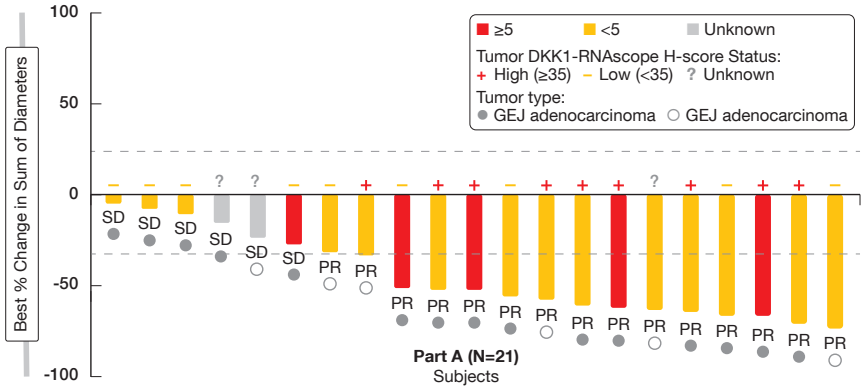

Figure 4: DisTinGuish Trial: best overall response by PD-L1 and DKK-1 Expression. CPS: visually-estimated combined positive score of PD-L1.

required a dose reduction and three discontinued the DKN-01 therapy.

Overall, DKN-01 in combination with tislelizumab plus chemotherapy was well tolerated and demonstrated a compelling ORR as a first-line treatment for advanced G/GEJ cancer.

Adjuvant tislelizumab in resected ESCC

Esophageal cancer (EC) is the sixth leading cause of cancer death worldwide, with ESCC being the most common subtype globally [19].

Chemoradiotherapy alone or chemoradiotherapy followed by surgery is a widely used standard of care for patients with ESCC but recurrence rates are high after a local therapy [20]. Recent data indicate that adjuvant immunotherapy might serve as a promising new treatment option in EC-patients with residual disease found at surgery after preoperative chemoradiotherapy [21].

At ESMO 2021, Kang et al. presented the study design of the randomized phase III trial AIRES/NCCES02 (ChiCTR2100045651), which aims to compare the efficacy and safety of postoperative chemotherapy combined with the anti-PD-1 antibody tislelizumab versus tislelizumab alone (for one year) in patients with resected ESCC at high risk for recurrence [22]. Key eligible criteria are the following: ≥18 years, ECOG PS ≤1, ESCC confirmed by histology, clinical stage II-IVA (stage II only includes cT2N1M0), nodal positive disease following neoadjuvant chemoradiotherapy or chemotherapy plus surgery or upfront surgery with R0 resection. Eligible patients will be randomly assigned to receive cisplatin-based doublets Q3W for two cycles, followed by tislelizumab (200 mg intravenously (IV), Q3W) for one year or tislelizumab (200 mg IV, Q3W) alone. Stratification will be performed according to the PD-L1 expression level, preoperative induction therapy, and postoperative infectious complications. Disease free survival (DFS) constitutes the primary endpoint, while secondary endpoints include OS, as well as safety and tolerability. Exploratory endpoints will investigate distant metastasis free survival and predictive biomarkers for AEs and recurrence. Approximately 220 patients will be enrolled in China; recruitment has started in May 2021.

INTEGRATE IIb: regorafenib + nivolumab

Tumor angiogenesis has been identified as a therapeutic target in GC. VEGF, a critical regulator of pathologic angiogenesis, is expressed in tumor tissue and peripheral blood. Regorafenib - a multikinase inhibitor (MKI) targeting VEGF, TIE-2, PDGF-β, RAF, RET and KIT - has shown efficacy in advanced GC; recent data demonstrated promising synergistic effects when combined with ICI [23, 24].

The ongoing phase III trial INTEGRATE IIb (NCT04879368) evaluates the impact of regorafenib combined with nivolumab in pretreated G/GEJ cancer [25]. Eligible patients have a metastatic or locally recurrent gastroesophageal cancer which has arisen in any primary gastroesophageal site (gastroesophageal junction or stomach) with adenocarcinoma or undifferentiated carcinoma histology, and with a minimum of two lines of prior anticancer therapy (at least one platinum agent and one fluoropyrimidine analogue). Exclusion criteria include prior VEGF TKI treatment (anti-VEGF monoclonal antibody treatement is permitted), bleeding disorders, uncontrolled CNS/brain metastases, and abnormal thyroid function. Patients will be stratified by geographic tumor region, prior VEGF inibition and prior immunotherapy, and randomly assigned 2:1 to receive regonivo (Regorafenib 90 mg orally, once daily on days 1-21 of each 28 day cycle; Nivolumab 240 mg IV, every 2 weeks) or a chemotherapy of investigator's choice (paclitaxel, docetaxel, irinotecan, or oral trifluidine/tipiracil).

Primary study endpoints are OS, while secondary endpoints include PFS, response rate, quality of life, toxicity, and exploratory correlative biomarkers. Approximately 450 adult patients are planned to be enrolled in 75 study locations in the U.S., Australia, Canada, Japan, Korea, New Zealand and Taiwan.

Novel anti-PD-1 pucotenlimab in second line G/GEJ cancer

Pucotenlimab (HX008) is a novel highly selective humanized anti-PD-1 antibody with a S228P hinge mutation and an engineered Fc domain. Pucotenlimab exhibits a decreased antibody-dependent cellular cytotoxicity (ADCC) and a complement-dependent cytotoxicity preventing depletion of PD-1-expressing lymphocytes, while retaining their antitumor activity [26, 27].

Phase I and II studies revealed durable antitumor activity of pucotenlimab in combination with chemotherapy in the first- and second line settings of G/GEJ cancer [28, 29]. Huang et al. presented at this year's ESMO meeting the study design of a currently ongoing randomized phase III trial (NCT04486651); this study is investigating the efficacy and safety of pucotenlimab plus irinotecan as 2L therapy in patients with advanced G/GEJ adenocarcinoma who have progressed after failure of the first-line treatment with platinum and/or fluoropyrimidine therapy [30]. Key inclusion criteria include histologically or cytologically confirmed unresectable or metastatic G/GEJ adenocarcinoma, ECOG ≤1, and adequate organ and hematopoietic functions. Stratification

will be performed according to ECOG PS, PD-L1 expression, and time to progression from first line treatment. Eligible patients are randomized to receive pucotenlimab (200 mg IV Q3W) plus irinotecan (160 mg/m^2 IV, Q2W) or placebo plus irinotecan (160 mg/m^2 IV, Q2W). OS will be primarily analyzed, while PFS, ORR, DCR, DOR and OS in PD-L1 CPS ≥ 10, as well as safety will be secondarily evaluated. The trial is currently recruiting patients in 64 Chinese centers.

Early results of zanidatamab in *HER2*-positive GI tumors

Zanidatamab (ZW25) is a novel bispecific antibody directed against HER2, that can simultaneously bind two non-overlapping epitopes, resulting in HER2 signal blockade [31]. Previously published data have shown promising and durable antitumour activity, as well as good tolerability, in patients with heavily pretreated advanced or metastatic *HER2*-expressing GEA or in G/GEJ adenocarcinoma [32].

The multicenter phase II trial (NCT03929666) was presented at ESMO 2021; this study investigated the safety, tolerability and anticancer activity of zanidatamab (30 mg/kg or 1800/2400 mg IV, Q3W) plus standard first-line combination chemotherapy in *HER2*-expressing GI tumors among patients in USA, Canada and Korea [33]. Of the 36 eligible patients, the primary tumor location was esophageal (n = 9), GEJ (n = 14), and gastric (n = 13); 89 % of patients were male, and 89 % showed *HER2*-positivity. Patients in the zanidatamab plus CAPOX group (n = 12) achieved a confirmed ORR (cORR) of 92 %. Eleven patients had a PR, and one patient a stable disease (SD), while mDoR was not reached (NR). Patients (n = 2) in the zanidatamab plus FP (5-FU and cisplatin) arm reached a cORR of 100 % with two CRs (mDoR, NR), while patients in the zanidatamab plus mFOLFOX6 cohort (n = 14) experienced a cORR of 57 % with one CR, seven PRs , three SDs and three progressive diseases (PDs), with a mDoR of 16.4 months. Across all treatment regimens, the cORR was 75 % with a mDoR of 16.4 months. With a median follow-up of 6.9 months, the mPFS reached twelve months and 61 % of patients were still on zanidatamab treatment.

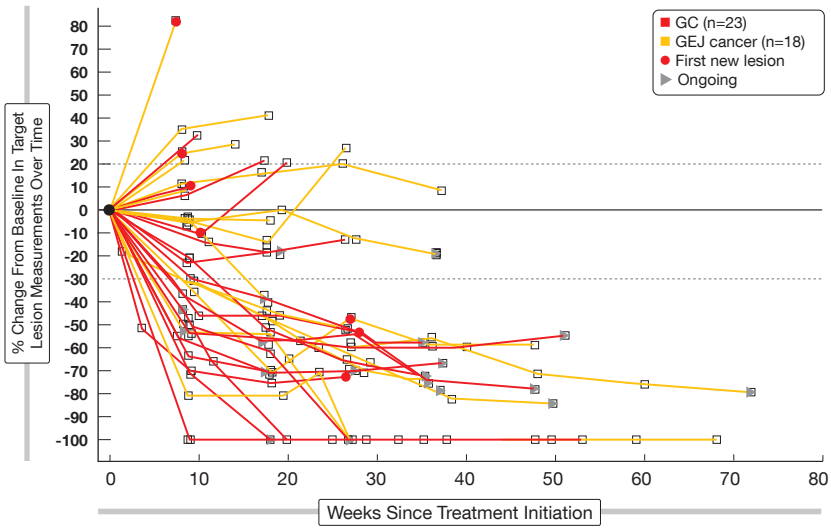

Figure 5: MAHOGANY trial: change in tumor size over time.

Treatment-emergent adverse events (TEAEs) were observed in 69 % of patients (n = 36) and consistent with previous reports. Diarrhea - the most frequent TEAEs (42 %) across treatment regimens - was manageable in the outpatient setting and mitigated by prophylaxis. No severe infusion related reactions or cardiac events were observed.

Based on these results, a global phase III study (HERIZON-GEA-01) will start its enrollment in 2021 to evaluate zanidatamab plus chemo (CAPOX or FP) in combination with the PD-1 inhibitor tislelizumab for the first-line treatment of *HER2*-positive GEA.

Margetuximab combined to retifanlimab in HER2+ GEJ cancer

Margetuximab, a chimeric, Fc-engineered, monoclonal antibody targeting the same epitope as trastuzumab, was approved in December 2021 by the U.S. FDA for pretreated *HER2*-positive patients with metastatic breast cancer [34]. Retifanlimab (also known as MGA012) is an investigational anti-PD-1 antibody being developed to be used either as monotherapy or in combination with other potential cancer therapeutics [35].

The combination of both agents, margetuximab and retifanlimab, is currently evaluated in the phase II/III MAHOGANY trial (NCT04082364) for the treatment of naïve patients with advanced GEJ adenocarcinoma [35]; first results of the cohort A were presented at ESMO 2021 [36]. This interim analysis included 43 patients (*HER2*-positiv, PD-L1 CPS ≥1) enrolled with gastric cancer (58.1 %) and GEJ cancer (41.9 %); most of them were male (90.7 %) and had a metastatic disease (83.7 %). Patients with central nervous system metastases were excluded. The best overall response (BOR) assessed by an independent review committee for the first 40 response-evaluable non-MSI-H patients was 52.5 % (n = 21). Four patients achieved a CR, 17 patients showed a PR, nine patients experienced a SD, and eight patients had a PD **(Figure 5)**. The mDoR was 10.3 months, while the mPFS reached 6.4 months, with a 12-month PFS rate of 50 %, and mOS was not reached (18-month OS rate, 85 %).

The combination was generally well tolerated. Treatment-related adverse events (TRAEs) occurred in 81.4 % of patients, mostly fatigue (21 %), infusion-related reaction (19 %), rash (19 %), diarrhea (16 %) and pruritus (16 %). Overall, 18.6 % of TRAEs were grade 3 to 4. To note, three patients discontinued the combination therapy because of irAEs (grade 3 renal function, grade 3 hepatitis and grade 1 diabetic ketoacidosis one each).

These study outcomes indicated that simultaneous targeting of HER2 and PD-1 (margetuximab plus retifanlimab) may be a potential option for the first-line therapy of *HER2*-positive patients with GEA.

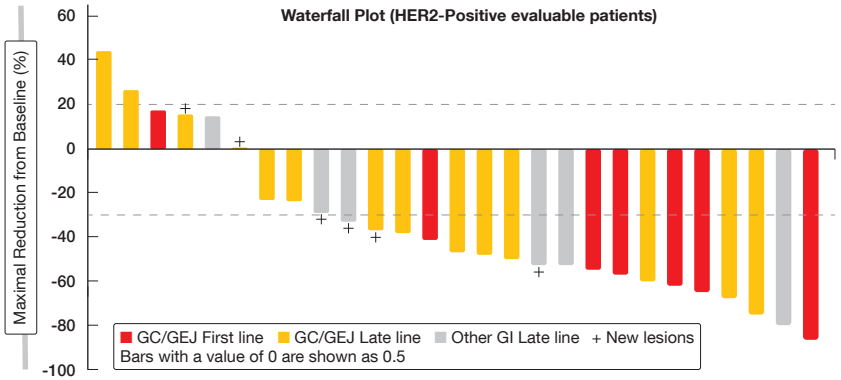

Figure 6: Waterfall plot of HER2-positive patients with GI tumors treated in first or later lines

Synergistic effects of PD-L1 and CTLA4 inhibitors

Combinations of ICI have shown encouraging progress in the treatment of various human cancers; however, the higher costs and greater side effects of such immune combinations compared with single-agent immunotherapies may limit their further applications [37]. Previous studies suggested potential synergetic effects of an immunotherapy combination in *HER2*-positive GEA patients [38].

KN046 - a novel bispecific antibody directed against PD-L1 and CTLA-4 - is delivered safely and effectively via a smart nano-delivery agent (ZIF-8) directly to the tumor area. KN046 was tested in combination with KN026, a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes. At ESMO 2021, preliminary results of a phase Ib dose escalation study (NCT04040699) with KN026 + KN046 in *HER2*-positive (IHC 3+ or HER2 gene amplification) patients with GI tumors were presented [39].

At the time of data cutoff (May 8, 2021), the dose-escalation and expansion study assigned 44 patients (68 % male, 77 % *HER2*-positive, 48 % previously HER2 treated) into four cohorts with different dose levels of KN026 and KN046 according to the study scheme. ORR reached 52 % (n = 27) in the overall *HER2*-positive group (GC/GEJ and other GI cancer), 71 % in the first-line G/GEJ cancer group (n = 7) and 43 % in ≥ 2 lines therapy G/GEJ cancer group (n = 14); DCR resulted in 85, 86 and 79 %, respectively **(Figure 6)**. The mDoR was eleven months in both overall *HER2*-positive group and ≥ 2 lines therapy G/GEJ cancer groups, and not estimable in the first-line cohort. In the overall group (n = 34), the PFS reached six months, 6-month PFS-rate (PFS-6m) was 40 % and 6-month OS-rate (OSR-6m) 93 %. In the first-line G/GEJ cancer group (n = 7), PFS was not reached, while PFS-6m and OSR-6m were 86 % and 100 %, respectively. The later lines G/GEJ cancer group (n = 17) achieved a PFS of four months, with a PFS-6m of 46 % and an OSR-6m of 93 %.

In total, 91 % of patients (n = 44) experienced TEAE; anemia (38.6 %), infusion related reaction (36.4 %), increased AST (27.3 %) and diarrhea (27.3 %) were the most commonly reported TEAEs. Grade ≥ 3 TEAEs occurred in eight patients, and the most common was anemia (4.5 %).

The combination of two different ICIs in combination with *HER2*-positive status emerged as a promising chemo-free regimen showing clinical efficacy and manageable side-effects. Pivotal trials in *HER2*-positive GC/GEJ patients are planned.

T-Dxd in HER2-positive G/GEJ cancer

About 20 % of advanced G/GEJ cancers show overexpression of human epidermal growth factor receptor 2 (HER2) [40]. Approved targeted therapies include anti-HER2 antibody trastuzumab in combination with chemotherapy in the first-line setting and VEGFR2 inhibitor ramucirumab in combination with paclitaxel as second line therapy. Acquired resistence and decreased HER2 expression remain a challenge, as well as the limited efficacy of ICI in this population [40, 41].

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate that delivers cytotoxic chemotherapy to cancer cells via a topoisomerase I inhibitor "payload" through a tetrapeptide-based linker attached to a HER2 monoclonal antibody binding to a specific target expressed on cancer cells. T-DXd is approved for pretreated *HER2*-positive advanced or metastatic GC in the US and Japan. Previous data from the DESTINY-Gastric01 trial demonstrated a clinically relevant antitumor activity of T-DXd in G/GEJ cancer patients in the third or later line of treatment [42]. The currently recruiting DESTINY-gastric04 (DG-04) study (NCT04704934) investigates T-Dxd in patients with *HER2*-positive GC or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen, and have not received any additional systemic therapy. The study design was presented at ESMO 2021 with OS as primary endpoint.

The key secondary endpoints include PFS, ORR, and immunogenicity of T-DXd. Patients are enrolled in 18 study locations in France, Japan, Korea and Singapore; estimated study completion date is November 2024 [43]. ■

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Highlights in cervical cancer

In 2020, more than 600,000 new cases of cervical cancer were diagnosed. Its mortality rate reached 57 % with more than 340,000 deaths; cervical cancer was the ninth leading cause of cancer-related death worldwide and therefore a concerning global health issue. In young women (aged 15 to 44 years), it is the second most common cancer and cause of cancer death [1]. So far, according to ESMO and NCCN guidelines, standard treatment for persistent, recurrent, or metastatic cervical cancer was a platinum-based chemotherapy [2, 3], the preferred regimen being platinum, paclitaxel and bevacizumab (in eligible patients) [4]. However, the immune checkpoint inhibitor (ICI) pembrolizumab has proven efficacy in the KEYNOTE-158 study as second-line monotherapy in patients previously treated for cervical cancer [5, 6].

Pembrolizumab plus chemotherapy: survival benefit in 1L

The protocol-specified first interim analysis of the randomized, double-blind, phase III study KEYNOTE-826 (NCT03635567) was presented at this year's virtual ESMO meeting [7]. This trial evaluated the benefit of adding the anti-PD-1 inhibitor pembrolizumab to a chemotherapy backbone (paclitaxel + cisplatin or carboplatin IV, Q3W for up to 6 cycles) with or without bevacizumab (15mg/kg IV, Q3W) for the first-line treatment of persistent, recurrent, or metastatic cervical cancer which was not curatively treatable. The dual primary endpoints were overall survival (OS) and progression-free survival (PFS) per RECIST v1.1 by investigator assessment; secondary endpoints enclosed objective response rate (ORR), duration of response (DoR), 12-month PFS and safety.

In both arms (pembrolizumab versus placebo), the median age of the study participants was approximately 50 years, with a majority of patients having squamous cell carcinoma (SCC) and around 30 % of them being in stage IVB at initial diagnosis. Overall, bevacizumab was used in more than 60 % of all

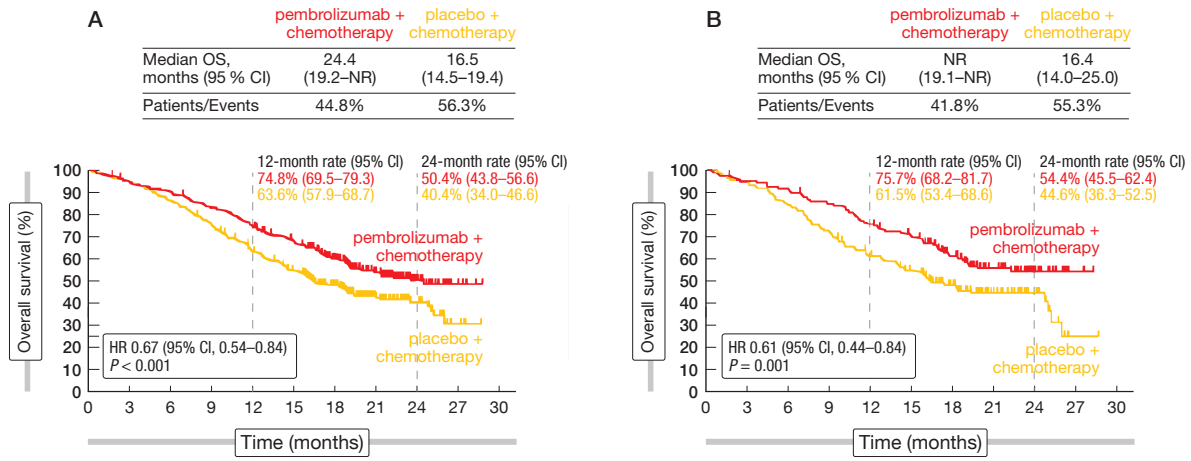

Figure 1: Overall survival in all-comer population **(A)** and in patients with high PD-L1 expression (CPS ≥10) **(B)**

patients during the study. Among the 617 patients randomized irrespectively of their PD-L1 status, a statistically significant improvement in the median PFS was reported for pembrolizumab versus placebo in the PD-L1 low combined positive score group (CPS ≥ 1; 10.4 vs 8.2 months; HR, 0.62; 95 % CI, 0.50-0.77; p<0.001), in the PD-L1 high-expressing group (CPS ≥ 10; 10.4 vs 8.1 months; HR, 0.58; 95 % CI, 0.44-0.77; p<0.001), as well as in the all-comer population (CPS ≥ 1; 10.4 vs 8.2 months; HR, 0.65; 95 % CI, 0.53-0.79; p<0.001). A PFS benefit was seen for all analyzed protocol-specified subgroups. Moreover, the pembrolizumab combination led similarly to a significantly longer median OS in the all-comer population (24.4 vs 16.5 months; HR, 0.67; 95 % CI, 0.54-0.84; p<0.001). Across subgroups defined by PD-L1 CPS, OS HRs were similar for pembrolizumab versus placebo in all comers (HR, 0.67), in those with PD-L1 CPS ≥1 (HR, 0.64) and in those with PD-L1 CPS ≥10 (HR, 0.61) **(Figure 1)**. In the overall study population, the ORR was 65.9 % in the combination arm versus 50.8 % in the placebo arm, while the DoR reached 18.0 versus 10.4 months, respectively.

The quality of life, as assessed through the EuroQol EQ-5D-5L VAS questionnaire, showed that the time to deterioration (time from first EQ-5D-5L VAS assessment to first onset of a ≥10-point decrease in score from baseline with confirmation under the right censoring rule or death, whichever occurred first) improved in the pembrolizumab arm (proportion of patients without deterioration at 12-month, 58.2 with pembrolizumab vs 44.8 % with placebo).

In total, the incidence of grade ≥3 adverse events (AEs) reached 81.8 % in the investigational arm compared to 75.1 % in the placebo arm, the most frequent ones being anaemia (30.3 % in the pembrolizumab group vs 26.9 % in the placebo group) and neutropenia (12.4 % versus 9.7 %, respectively).

A clinically significant benefit of the combined therapy (pembrolizumab + chemotherapy) was observed, regardless of the addition of bevacizumab and of the PD-L1 status at initial diagnosis. The authors concluded that pembrolizumab plus chemotherapy (with or without bevacizumab) may be a new 1L standard option for women with persistent, recurrent, or metastatic cervical cancer. Based on the outcomes of the KEYNOTE-826 study, this combination therapy was approved by the US FDA in the first-line setting; this led thus to an accelerated approval of pembrolizumab monotherapy in the second-line setting. Both first- and second-line FDA approvals of pembrolizumab concerned only patients presenting with a PD-L1 CPS score of 1 or greater.

EMPOWER-Cervical 1: cemiplimab versus chemotherapy

After progression on standard first-line therapy (platinum-based chemotherapy ± bevacizumab), salvage chemotherapy does not result in survival benefit for patients with recurrent or metastatic cervical cancer [8-11]. EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 is an open-label, randomized, multicenter, phase III study (NCT03257267) evaluating the efficacy and safety of cemiplimab monotherapy versus investigator's choice chemotherapy in this population in 2L or 3L setting. The preliminary results were presented at ESMO 2021 meeting [6]. In total, 608 patients with recurrent or metastatic cervical cancer who progressed after 1L treatment were randomized (1:1) regardless of PD-L1 expression to receive either cemiplimab (350 mg IV, Q3W) or a chemotherapy regimen up to 96 weeks.

At baseline, the median age of the patients was 51 years, most of them were less than 65 years old and presented with a metastatic disease. At the interim analysis, the median OS - the primary endpoint - for the overall population was superior in the cemiplimab arm compared to the chemotherapy arm (12.0 vs 8.5 months; HR, 0.69; 95 % CI, 0.56-0.84; p=0.00011). In the SCC population, a similar advantage was observed for the investigational group (11.1 vs 8.8 months; HR, 0.73; 95 % CI, 0.58-0.91; p=0.00306), whereas the adenocarcinoma group seemed to benefit the most from this anti-PD-1 therapy (13.3 vs 7.0 months; HR, 0.56; 95 % CI, 0.36-0.85; p<0.005). In all analyzed prespecified subgroups, OS data favored cemiplimab. Although patients with PD-L1 expression ≥1 % showed a larger

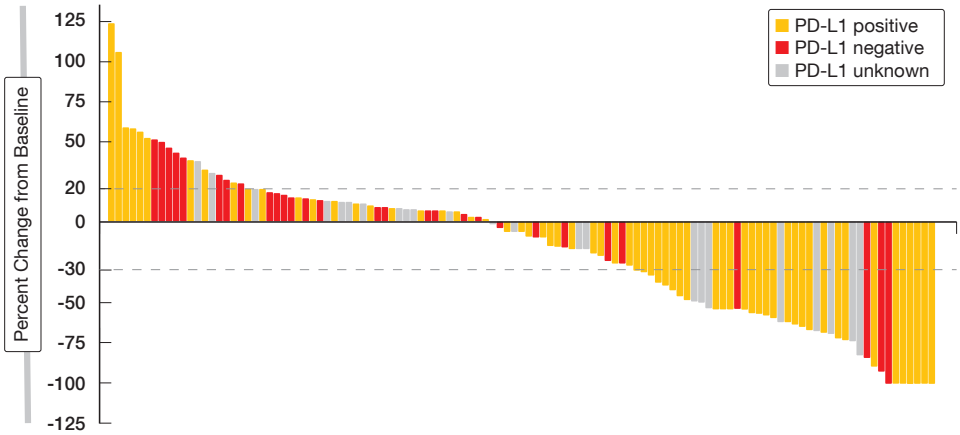

Figure 2: Waterfall plot of the C-550 study according to PD-L1 expression

OS benefit, patients with PD-L1 <1 % profited from the ICI therapy too. ORR benefit was observed in the overall and adenocarcinoma population, regardless of PD-L1 status.

Concerning the quality of life of the study patients, patients who received cemiplimab improved or maintained their global health status from baseline compared to those who were treated by chemotherapy.

Most common grade ≥3 treatment-emergent adverse events (TEAEs) for cemiplimab versus chemotherapy were anemia (12.0 vs. 26.9 %), asthenia (2.3 vs. 1.0 %), fatigue (1.3 vs. 1.4 %) and neutropenia (1.0 vs. 9.0 %). Discontinuation due to grade ≥3 TEAEs occurred in 6.7 % (cemiplimab) and 3.8 % (chemotherapy) of patients.

Cemiplimab showed a favorable toxicity profile and an OS superiority versus chemotherapy for the treatment of patients with recurrent or metastatic cervical cancer regardless of the PD-L1 expression. Although it is not yet approved for the treatment of cervical cancer, the PDUFA date for cemiplimab in this setting is set for end of January 2022.

Balstilimab (anti-PD-1) combined to zalifrelimab (anti-CTLA-4)

The second-line treatment of recurrent or metastatic cervical cancer is still very challenging. In many malignant solid entities, the combination of PD-1 and CTLA-4 inhibitors has proven to be efficient. The aim of the global phase II study C-550 (NCT03495882) was to evaluate the efficacy and safety of the dual blockade of balstilimab - an anti-PD-1 agent - and zalifrelimab – an CTLA-4 inhibitor. While the preliminary results were shown at last year's ESMO meeting [12], Dr. O'Malley presented the final data at ESMO 2021 [13]. Eligible patients had a measurable disease, a good ECOG performance status (0-1) and a histologically confirmed SCC, adenosquamous carcinoma or adenocarcinoma of the cervix which relapsed after platinum-based treatment. The 155 enrolled patients were administered balstilimab (3 mg/kg, Q2W) and zalifrelimab (1 mg/kg, Q6 W) for up to 24 months. The primary endpoint was ORR by RECIST v1.1 per independent review committee, while the DoR, PFS and OS were secondarily analyzed.

The patients had a median age of 50 years (24-76) and presented predominantly with SCC tumor histology (70.3 % of patients). At this final analysis, the ORR reached 25.6 %, with ten complete responses (CRs) and 22 partial responses (PRs) **(Figure 2)**; the ORR was 32.8 % among PD-L1-positive patients and 9.1 % in the PD-L1-negative group. The median DoR was not reached, whereas the 6-month DoR was 86.5 % and the 12-month DoR 64.2 %. After a median duration of follow-up of 21 months, the median PFS was 2.7 months (95 % CI, 1.5-3.7) and the median OS 12.8 months (95 % CI, 8.8-17.6). Moreover, in the PD-L1 expressing population, the median OS reached 15.7 months (95 % CI, 7.6-21.1).

No new safety signals were identified with this combined therapy. Overall, 31 patients (20.0 %) experienced grade ≥3 TEAEs, most frequently ALT elevation (2.6 %) and diarrhea (1.9 %). Treatment discontinuations due to a TEAE occurred in 19 pts (12.3 %). In total, 69 patients (44.5 %) had immune-related AEs (irAEs) any grade, most commonly hypothyroidism (14.2 %), hyperthyroidism or diarrhea (each 7.1 %), and pruritus (4.5 %).

Balstilimab plus zalifrelimab exhibited a durable efficacy and a manageable tolerability in the largest study to date investigating this dual combina-

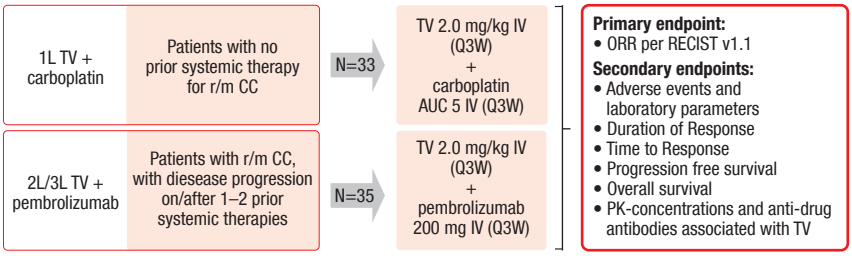

Figure 3: Study design of the ENGOTcx8/GOG 3024 innovaTV 205 trial

tion in recurrent or metastatic cervical cancer. Thus, this new regimen constitutes a novel promising 2L therapeutic option for those pretreated patients.

Efficacy of tisotumab vedotin in several clinical settings

Tisotumab vedotin, an antibody drug conjugate that targets tissue factor, is currently under development for the treatment of a broad range of solid tumors [14]; it already showed an antitumoral activity and a manageable safety profile in a pivotal, single-arm, phase II trial in patients with pretreated recurrent or metastatic cervical cancer, a patient collective presenting an unmet need for efficient therapies [15]. The first data regarding the combination of tisotumab vedotin with pembrolizumab, carboplatin, and bevacizumab in this population have already been shown at the IGCS 2021 meeting [16]; Dr. Vergote presented the outcomes of two further cohorts (1L tisotumab vedotin + carboplatin and 2L/3L tisotumab vedotin + pembrolizumab) at this year's ESMO 2021 [17].

The design of the multicohort phase Ib/II trial ENGOT-cx8/GOG-3024/innovaTV 205 (NCT03786081) evaluating the efficacy and safety of both dose expansion cohorts with tisotumab vedotin is described in **Figure 3**. The primary endpoint was the ORR per RECIST v1.1, while the secondary endpoints included safety, DoR, time to response, PFS and OS. At the time of the study enrollment, the median age of patients was 51.0 years for tisotumab vedotin plus carboplatin versus 47.0 years in the tisotumab vedotin plus pembrolizumab arm; most of the patients presented with a squamous tumor histology.

For the first-line therapy (tisotumab vedotin + carboplatin), the confirmed response rate (ORR) was 55 % (95 % CI, 36-72), including four CRs and 14 PRs. The median DoR was 8.3 months (95 % CI, 42-NR); the median PFS was 9.5 months (95 % CI, 4.0-NR) and the median OS has not yet been reached. In this study group, grade ≥3 AEs related to tisotumab vedotin occurred in 57.6 % of patients and serious AEs (SAEs) related to the investigational drug were reported in 15.2 % of them.

In pretreated patients who received tisotumab vedotin plus pembrolizumab as second- or third-line treatment, the ORR reached 38 % (95 % CI, 22-56, including 2 CRs and 11 PRs), while the median DoR was 13.8 months (95 % CI, 2.8-NR), the median PFS 5.6 months (95 % CI, 2.7-13.7) and the median OS not available so far. Overall, 45.7 % of patients experienced grade ≥3 AEs related to tisotumab vedotin and 14.3 % of them SAEs associated with the investigational drug.

Despite the small sample size of the study groups in this early-phase clinical trial, both arms (1L and 2L/3L) showed promising and durable antitumoral activity, with an acceptable safety profile. A further dose expansion cohort of tisotumab vedotin plus pembrolizumab as first-line treatment of recurrent or metastatic cervical cancer is currently under evaluation. In the second- or third-line of treatment, tisotumab monotherapy was approved shortly before pembrolizumab; to note, the use of tisotumab is not biomarker-restricted. ■

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Emerging landscape and treatment options in breast cancer

Breast cancer (BC) is the most common malignancy and the leading cause of cancer death worldwide in women; in 2020, almost 2.3 million people were diagnosed, and more than half a million died from BC [1]. Triple-negative breast cancer (TNBC), a subtype of BC lacking the expression of two hormone receptors (HR) (estrogen receptor [ER], progesterone receptor [PR]), and human epidermal growth factor receptor type 2 [HER2], affects approximately every sixth BC patient and is associated with a poor prognosis, an early relapse, and a high frequency of lung, liver and brain metastases [2].

Final analysis of KEYNOTE-355

Pembrolizumab, a humanized anti-PD-1 monoclonal antibody, showed encouraging antitumor activity across different tumor entities, including metastatic TNBC (mTNBC) [3-6]. The KEYNOTE-355 trial (NCT02819518) was the first phase III study evaluating an anti-PD-1 immunotherapy against mTNBC that showed a significant and clinically meaningful improvement in progression-free survival (PFS) among patients with PD-L1-positive (CPS ≥ 10) disease [6]. Based on these results, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved pembrolizumab in November 2020 and in October 2021, respectively, for the first-line treatment of patients with locally recurrent unresectable or mTNBC whose tumors express PD-L1 with a CPS ≥ 10 [7, 8]. The final results from the KEYNOTE-355 clinical trial were presented at ESMO 2021 [9].

Patients were randomized (2:1) to either pembrolizumab plus chemotherapy (taxane or gemcitabine-carboplatin) or placebo plus chemotherapy. Exclusion criteria were administration of systemic steroids, active central nervous system (CNS) metastases, and active autoimmune disease. Patients' characteristics were well-balanced between the pembrolizumab group (n = 566) and the control arm (n = 281), in terms of age, ECOG PS 1, CPS status, and use of taxane chemotherapy. The co-primary endpoints were PFS and OS in patients with PD-L1-positive tumors. A benefit of the addition of pembrolizumab to the chemotherapy backbone was particularly observed for the PD-L1 CPS ≥ 10 group, in whom PFS and OS were both significantly improved. After a median follow-up of 44.1 months, the combined therapy resulted in a median PFS (mPFS) of 9.7 months and a mOS of 23.0 months in the pembrolizumab arm versus 5.6 and 16.1 months in the control arm, respectively **(Figure 1)**. Pembrolizumab plus chemotherapy reduced the risk of death by 27 % (HR, 0.73; 95 % CI, 0.55-0.95; p = 0.0093) as compared to chemotherapy alone. The objective response rate (ORR) reached 52.7 % in the pembrolizumab arm versus 40.8 % in the control arm; disease control rate (DCR) was 65.0 % versus 54.4 %, respectively.

Although for patients with PD-L1 CPS ≥ 1 a significant benefit was observed for PFS (mPFS, 7.6 vs 5.6 months), only a trend was observed for OS (mOS, 17.6 vs 16.0 months; p = 0.0563). ORR reached 44.9 versus 38.9 % and DCR 58.6 versus 53.6 %, respectively. A similar trend was observed in the overall population (ITT), where mPFS was 7.5 versus 5.6 months, and mOS reached 17.2 versus 15.5 months. In the ITT, the ORR was 40.8 versus 37.0 %, and DCR was 56.0 % versus 51.2 %. Duration of response (DoR) was higher in the PD-L1 CPS ≥ 10 subset (PD-L1 CPS ≥ 10, 12.8 vs 7.3 months; PD-L1 CPS ≥ 1, 10.1 vs 6.8 months; ITT, 10.1 vs 6.5 months).

No new safety signals were identified. The most common treatment-related adverse events (TRAEs) were anemia (49.1 % in the pembrolizumab + chemotherapy group vs 45.9 % in the placebo + chemotherapy group), neutropenia (41.1 % vs 38.1 %), and nausea (39.3 % vs 41.3 %). TRAEs of grade 3 to 5 occurred in 68 % of patients in the investigational arm and 67 % of those in the control arm.

The KEYNOTE-355 study has met both co-primary endpoints. The authors concluded that these results support the use of pembrolizumab in combination with chemotherapy as a new standard of care for patients with locally recurrent

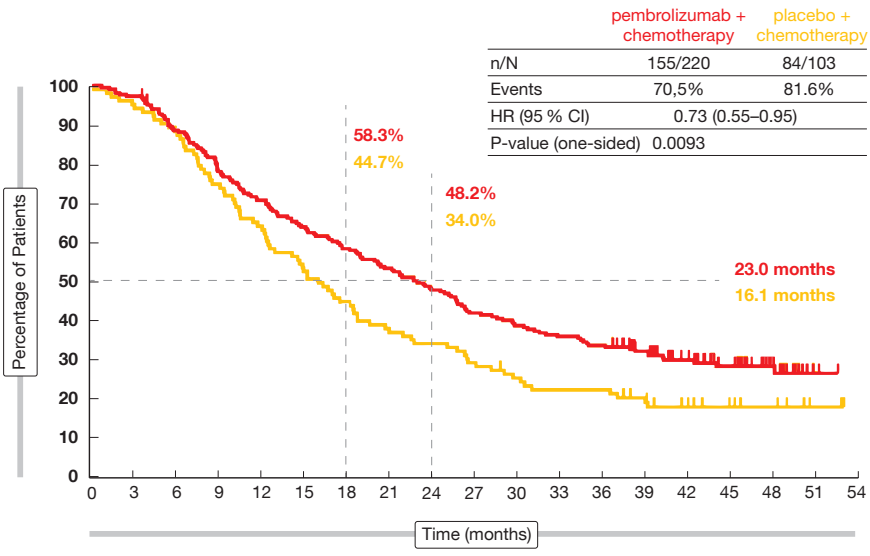

Figure 1: Median OS in the PD-L1 CPS ≥ 10 patient population of the KEYNOTE-355 trial

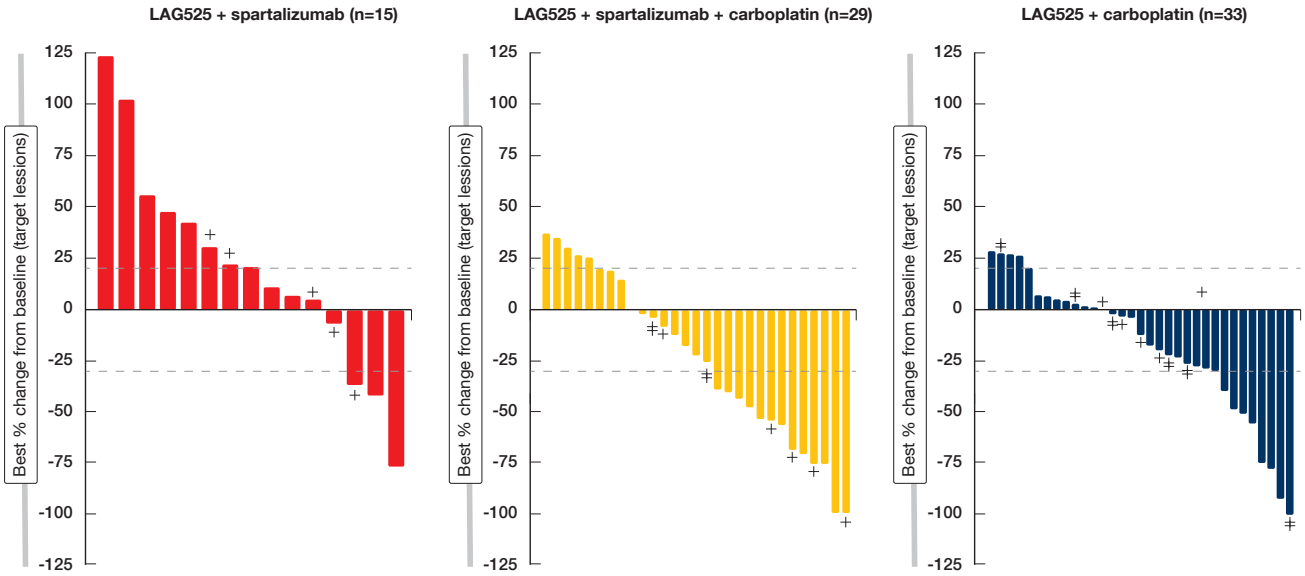

Figure 2: Best percentage change of the targeted lesions from baseline per RECIST v1.1 in each study arm.

unresectable or metastatic TNBC whose tumors express PD L1 (CPS ≥ 10).

Dual immune checkpoint blockade in TNBC

Preclinical studies showed synergistic antitumor effects when combining PD-1 and LAG-3 inhibition [10, 11], as well as an enhancement of treatment efficacy when using chemotherapy plus immunotherapy in patients with advanced TNBC [12, 13]. A phase II study (NCT03499899) presented at this year's ESMO meeting examined the efficacy and safety of the anti-PD-1 antibody spartalizumab combined with the LAG-3 inhibitor LAG525 in addition to chemotherapy [14].

A total of 88 checkpoint inhibitor (CPI) naïve female patients with advanced TNBC and ≤1 prior line of systemic treatment were randomized (1:1:1) into three arms: LAG525 (400 mg IV, Q3W) + spartalizumab (300 mg IV, Q3W); LAG525 + spartalizumab + carboplatin (AUC6 IV Q3W); or LAG525 + carboplatin. Following the premature closure of the LAG525 + spartalizumab arm due to increased progressive disease, subsequent enrolled patients were randomized (1:1) into both other arms. The primary endpoint was ORR per RECIST v1.1.

In the LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin, or LAG525 + carboplatin group, the median age was 57.0/50.0/53.5 years and 50.0/23.5/41.2 % presented with an ECOG PS ≥ 1. Almost all patients had a metastatic disease, whereas more than half of the enrolled subjects were first-line patients. After a median follow-up of 12.5 months, no treatment arm met the primary endpoint (ORR per RECIST v1.1 analyzed when all pts had ≥24 weeks follow-up or discontinued tumor assessments for any reason. Proof of preliminary efficacy required both a posterior mean ORR ≥35 % and a posterior probability of (ORR ≥25 %) ≥90 %. Further efficacy outcomes and safety were secondary endpoints). In the triplet combination arm (n=34), the ORR reached 32.4 % with five patients achieving a complete response (CR); the ORR in the LAG252 + carboplatin group (n=34) was 17.6 %. Tumor shrinkage was observed in 20/69/61 % of the LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin, and LAG525 + carboplatin group, respectively, **(Figure 2)**. A high ORR (47.4 %) was seen in patients receiving the triplet regimen in the first-line setting (n=19). Although data should be interpreted with caution due to the small number of patients, an exploratory subgroup analysis revealed higher ORRs in PD-L1-positive, LAG3-positive, and CD8-positive patients treated with the triplet combination compared to each duplet therapy. Median PFS resulted in 1.4/4.3/3.0 months and mOS in 6.1/11.6/8.0 months in the LAG525 + spartalizumab, LAG525 + spartalizumab + carboplatin, and LAG525 + carboplatin group, respectively.

The most common grade ≥ 3 AEs (in %) were anemia (0/26.5/20.6), platelet count decreased (5.3/20.6/5.9), thrombocytopenia (0/23.5/11.8) and neutrophil count decreased (0/23.5/5.9) in the LAG525 + spartalizumab arm, LAG525 + spartalizumab + carboplatin and LAG525 + carboplatin arm, respectively. The study of LAG525 in combination with spartalizumab and/or carboplatin in patients with an advanced TNBC did not meet its primary endpoint, thus no further clinical investigation is planned.

DESTINY-Breast03: antibody-drug conjugates in HER2+ mBC

HER2 positive breast cancer (HER2+ BC) accounts for 14 % of all female breast cancer cases [15]. Traditionally associated with a poor prognosis [16], patients with HER2+ BC benefitted from the development of HER2-targeted therapy [17]. The monoclonal antibodies trastuzumab and pertuzumab, in combination with taxane and the antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1), are well es-

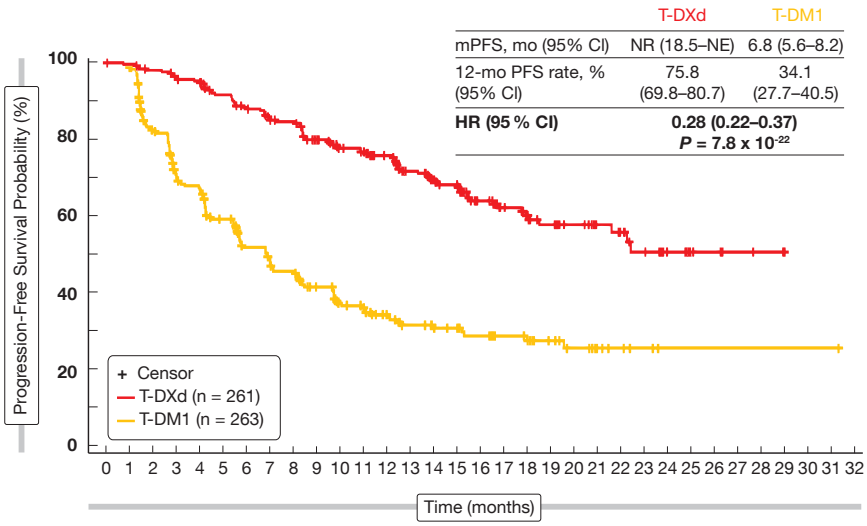

Figure 3: PFS as assessed by blind independent central review (BIRC) in the DESTINY-Breast03 study

tablished systemic treatment strategies in the first- and second-line therapy of HER2+ mBC [18]. Recent studies evaluating oral tyrosine kinase inhibitors (TKIs), such as tucatinib and neratinib, as well as ADCs like trastuzumab deruxtecan (T-DXd) showed further improvements in this patient population [18].

The phase II DESTINY-Breast01 trial (NCT02564900) already showed a robust antitumor activity of T-DXd in the third-line treatment of HER2+ mBC (mPFS, 19.4 months; ORR, 61.4 %; estimated 12-months OS, 85 %) [19, 20]. Based on these results, T-DXd received U.S. FDA and EMA approval for its use in patients with unresectable or metastatic HER2+ BC following two or more prior anti-HER2-based regimens [21, 22].

The head-to-head, randomized, phase III DESTINY-Breast03 (NCT03529110) study evaluated T-DXd versus T-DM1 in patients with HER2+ mBC previously treated with trastuzumab and a taxane; the results were presented at ESMO 2021 [23]. The global trial randomized (1:1) 524 females with unresectable or metastatic HER2-positive breast cancer to either receive T-DXd (5.4 mg/kg, Q3W) or T-DM1 (3.6 mg/kg, Q3W). Patients who had progressed within six months after the end of (neo)adjuvant treatment including trastuzumab and a taxane were allowed. The median age was 54 years; more than half of the patients were Asian, about one fifth of patients had a history of brain metastases and 70 % had visceral disease at enrollment.

The interim analysis with data cutoff of May 21, 2021, showed that T-DXd significantly improved the progression-free survival (PFS) – the primary endpoint assessed by blind independent central review (BIRC) – compared with T-DM1 (not yet reached vs 6.8 months; HR, 0.28; 95 % CI, 0.22-0.37; p = 7.8 x 10^{-22}); the 12-month PFS rate was 75.8 % for T-DXd versus 34.1 % for T-DM1 **(Figure 3)**. Improved efficacy with T-DXd was shown across all prespecified subgroups including hormone receptor status, prior pertuzumab treatment, presence of visceral disease, number of prior therapy-lines, and presence/absence of brain metastases.

The median OS was not estimated (NE) in both arms (HR, 0.56; 95 % CI, 0.36-0.86; p = 0.007172) and the 12-month OS rates were 94.1 % in the T-DXd arm versus 85.9 % in the T-DM1 arm. Confirmed ORR was 79.7 % for T-DXd (16.1 % with a complete response [CR], 63.6 % with a partial response [PR]) versus 34.2 % for T-DM1 (8.7 % with a CR, 25.5 % with a PR). Median follow-up was 16.2 months for T-DXd and 15.3 months for T-DM1. At the time of this interim analysis, more than 50 % of patients remained on T-DM1 (n = 132) compared with 18 % on T-DM1 (n = 47).

In terms of safety, grade ≥ 3 TRAEs occurred in 45.1 % of patients treated with T-DXd versus 39.8 % of those in T-DM1 arm. As AE of special interest, interstitial lung disease (ILD) was reported with grades 1 to 3 in 10.5 % of patients in T-DXd arm and 1.9 % in those in T-DM1 arm; moreover, no grade 4 or 5 adjudicated drug related ILD/pneumonitis events were observed in either arm. The most frequent TEAEs leading to treatment discontinuation were (ILD)/pneumonitis (8.2 %) with T-DXd and thrombocytopenia (2.7 %) with T-DM1.

These data demonstrated a significant superiority of T-DXd over T-DM1 and thus support T-DXd becoming the standard of care (SOC) for the second-line treatment of HER2+ mBC.

DESTINY-Breast09: 1L T-DXd in HER2+ mBC

In patients with HER2+ mBC, taxane plus trastuzumab plus pertuzumab - the standard first-line triple therapy - demonstrated high mPFS and mOS [24]; however, following this treatment, resistance was emerging. Therefore, new therapeutic options are needed to delay the development of resistance and thus extend the overall survival of patients in 1L setting.

DESTINY-Breast09 (NCT04784715) is a global, randomized, phase III ongoing study aiming to evaluate the safety and efficacy of T-DXd (5.4 mg/kg) with or without pertuzumab compared with SOC (taxane [docetaxel or paclitaxel], trastuzumab and pertuzumab) as first-line treatment in patients with HER2+ (IHC 3+ or ISH+) mBC; the study design was presented at ESMO 2021 **(Figure 4)** [25]. Randomization is 1:1:1 to receive either T-DXd as a monotherapy with a pertuzumab-matching placebo, T-DXd in combination with pertuzumab or SOC. Randomization will be stratified by prior treatment (de novo versus recurrent), HR status and PIK3CA mutation status (detected versus not detected).

The primary endpoint of DESTINY-Breast09 is PFS by BIRC, while secondary endpoints include OS, ORR, DoR, pharmacokinetics, health-related quality of life (HR-QoL) and safety. The study plans to recruit more than 1,100 patients; enrollment started in April 2021 and recruitment is currently ongoing in 298 study locations worldwide.

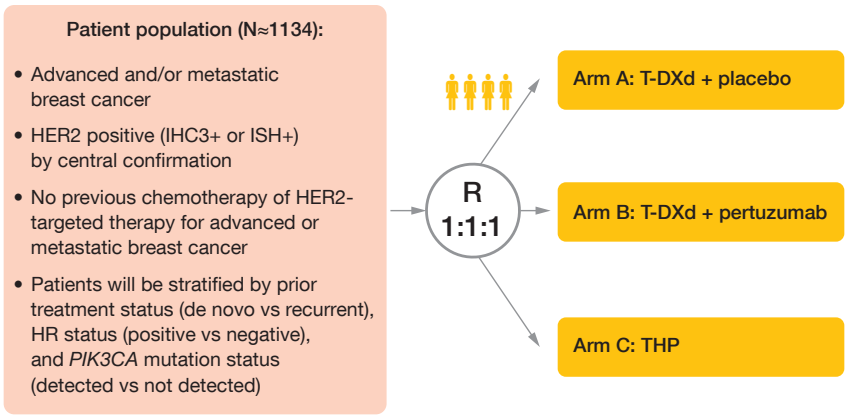

Figure 4: Study design of DESTINY-Breast09 in HER2+ (IHC 3+ or ISH+) mBC

Neo-LaTH (JBCRG-16) study: long-term follow-up

Dual HER2 blockade with trastuzumab has been shown to produce a greater survival benefit compared with trastuzumab alone; several studies in the neoadjuvant setting for HER2+ BC reported improved efficacy by adding dual HER2 blockade to chemotherapy [26]. Both NeoSphere (trastuzumab plus pertuzumab) and NeoALTTO (TKI lapatinib plus trastuzumab) studies reported a significantly increased pathological complete response (pCR) rate [26]. The phase II Neo-LaTH study (JBCRG-16) (UMIN000007576) randomized Japanese patients with HER2+ primary BC (T1c-3 N0-1 M0; target lesion ≤7 cm), aged 20 – 70 years with no prior therapy for breast cancer evaluate the efficacy and safety of lapatinib and trastuzumab (6 w) followed by lapatinib and trastuzumab plus weekly paclitaxel (12 w) with/without prolonged anti-HER2 therapy prior to chemotherapy (18 vs. 6 w), and in ER positive (ER+) patients, with/without endocrine therapy, for the treatment of HER2+ primary breast cancer [27]. As reported previously, comprehensive pCR rate (CpCR, ie. no residual tumor or residual ductal carcinoma in situ) - the primary endpoint - was achieved in 101 patients (47.9 %) and was significantly higher in ER-negative (ER-) than in ER+ patients (ER-, 63.0 %; ER+, 36.1 %; p = 0.0034). Overall, pCR with pN0 was achieved in 42.2 % of patients (ER-, 57.6 %; ER+, 30.3 %) [27]. At this year's ESMO meeting, long-term 5-year follow-up data, after successful surgery, of the Neo-LaTH study were reported [28].

The disease-free survival (DFS) rate was 87.8 % and higher in patients who achieved CpCRypN0 (i.e., comprehensive pathological complete response with a pathologically negative axilla) after neoadjuvant treatment. Among non-pCR patients, G2b (defined as only focal invasive tumor residues confirmed in the removed breast tissue; near pCR) was confirmed in nine of 35 ER- patients and in eleven of 78 ER+ patients. Adjuvant anthracycline therapy was given in 48.6 %. In the ER+ cohort, the 5-year distant DFS rate ranged between 90 to 93 % in patients who did not achieve CpCRypN0, regardless of use of adjuvant A. Moreover, it should be taken into account that brain metastases did occur in some cases, even in patients who achieved CpCRypN0.

Neoadjuvant induction of dual HER2 blockade therapy with trastuzumab and lapatinib combined with paclitaxel resulted in a higher 5-year DFS rate in patients who achieved CpCRypN0 after neoadjuvant treatment compared with those who did not. Omission of adjuvant anthracycline therapy may thus be considered in patients who achieved CpCRypN0 after neoadjuvant treatment.

KATE3: ADC combined with PD-L1 inhibition

An exploratory analysis of the KATE2 study – the first randomized phase II trial investigating the use of T-DM1 plus atezolizumab in HER2+ advanced BC - suggested a survival benefit for patients with PD-L1-positive tumors treated with the dual therapy; however, the magnitude of the effect remained unclear because of small sample sizes and imbalances in baseline prognostic factors [29]. At ESMO 2021, the study design of KATE3 (NCT04740918), an ongoing phase III study to evaluate the efficacy and safety of T-DM1 with atezolizumab or placebo in patients with centrally-determined HER2-positive and PD-L1 positive unresectable locally advanced BC (laBC) or mBC patients who received prior trastuzumab (± pertuzumab) and taxane-based therapy, was presented [30].

Study participants must have progressed either during or after prior trastuzumab (+/- pertuzumab) and taxane-based therapy for laBC or mBC, or during (or within 6 months after completing) trastuzumab (+/- pertuzumab) and taxane-based therapy in the neoadjuvant and/or adjuvant setting. Eligible patients are randomized (1:1) to 3-weekly cycles of T-DM1 (3.6 mg/kg) and atezolizumab (1200 mg) or T-DM1 (3.6 mg/kg) and placebo. Approximately 350 patients will be enrolled at approximately 175 sites worldwide and stratified by hormone receptor status, disease status, and world region. PFS (investigator assessed) and OS constitute the co-primary endpoints, while secondary endpoints include ORR, DoR, as well as OS and PFS in patients with baseline brain metastases, central nervous system PFS, patient-reported outcomes, and safety.

coopERA Breast Cancer: next generation SERD in ER+/HER2- BC

HR+/HER2- is the most common subtype of breast cancer, with an age-adjusted rate of 88.1 new cases per 100,000 women [15]. Endocrine therapy (ET) - including selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), or selective estrogen receptor degraders (SERDs) - is the backbone to treat advanced ER+ BC [31]; however, drug resistance remains a challenge [31]. The only approved SERD, fulvestrant, has to be administered through an intramuscular injection and presents poor pharmacokinet-

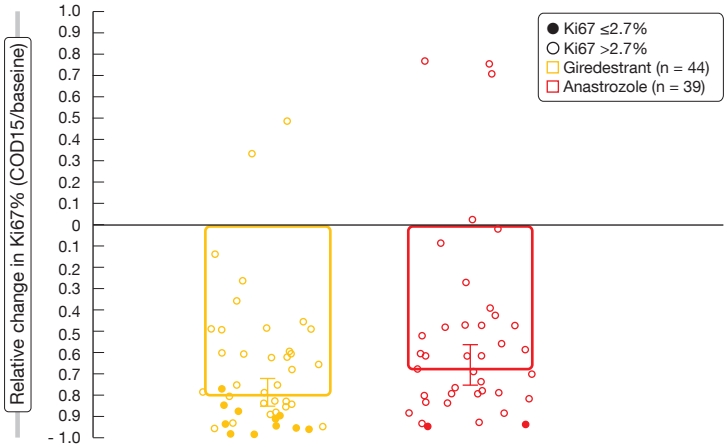

Figure 5: coopERA Breast Cancer trial: relative reduction in Ki67 with giredestrant and anastrozole at Week 2

ics [32]. Giredestrant, a next generation investigational SERD, already showed a promising antitumor activity in mBC, either as monotherapy or in combination with the CDK4/6 inhibitor palbociclib [33].

The neoadjuvant phase II study CoopERA Breast Cancer (NCT04436744) evaluated giredestrant versus anastrozole in ER+/HER2- untreated BC (locally assessed). Results from a preplanned interim analysis were presented at ESMO 2021 [33]. At the data cut-off of April 9, 2021, this trial enrolled 202 untreated ER+/HER2- BC postmenopausal women whose tumor was at least 1.5 cm at the time of presentation and who had a baseline Ki67 score of 5 % or greater. A total of 109 patients were already randomized (1:1) to receive a daily oral dose of either giredestrant (30 mg) or anastrozole (1 mg) during a 2-week window of opportunity phase. Patients then received 16 cycles (days 1-28, 28 days each) of either giredestrant or anastrozole at the same dose, combined with oral palbociclib at a daily dose of 125 mg (days 1-21) pre-surgery.

Patients' characteristics were well balanced with a median age of 65 years in the giredestrant arm and 62 years in the anastrozole arm; in both arms, most patients had a stage IIA disease (45 % versus 38 %), a nodal status of N0 (56 % versus 49 %), and a tumor status of T2 (65 % vs 62 %) at diagnosis, respectively. Among the 83 patients assessed in the interim analysis, giredestrant showed a mean Ki67 reduction - the primary endpoint - of 80 % versus 67 % for anastrozole during the window of opportunity phase (1-14 days) **(Figure 5)**. In total, 25 % of tumors exhibited a complete cell cycle arrest rate (CCCA) with giredestrant versus 5 % with anastrozole. Consistent Ki67 suppression was observed in patients with baseline Ki67 ≥ 20 % (83 % reduction with giredestrant vs 71 % with anastrozole) or baseline Ki67 < 20 % (65 % vs 24 %, respectively).

Safety results were consistent with the known safety profile of giredestrant, with fewer patients experiencing AEs related to giredestrant (28 %) versus anastrozole (38 %); the most common AEs were arthralgia (5.7 % versus 10.9 %), decreased blood cell count (3.8 % versus 9.1 %), bradycardia (5.7 % versus none), and vomiting (5.7 % versus none). No grade ≥ 3 AEs or serious AEs (SAEs) were associated with giredestrant.

This is the first randomized study showing a superior antiproliferative activity of an oral SERD over an aromatase inhibitor and with a favor-

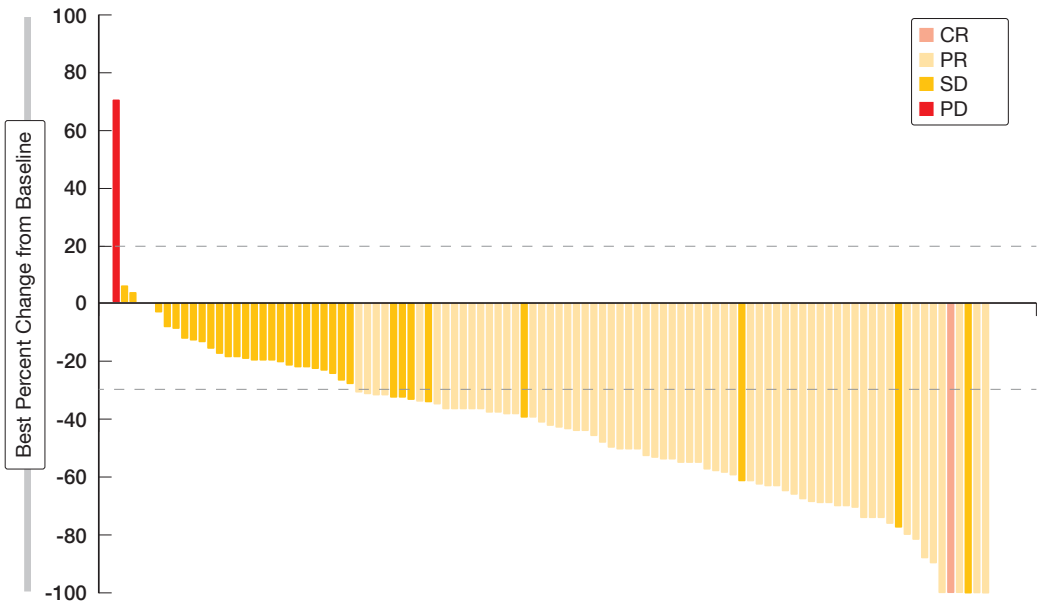

Figure 6: Waterfall plot outlining the investigator's assessed best overall response of the EN cohort in the MONARCH 2 study.

able safety profile in HR+/HER2- BC. Giredestrant is currently being investigated in further phase III studies evaluating its efficacy in ER+/HER2- la/mBC patients versus letrozole (persevERA Breast Cancer, NCT04546009) and in the adjuvant setting versus ET of physician's choice (lidERA Breast Cancer, NCT04961996).

MONARCH 2: CDK4/6 inhibition in HR+/HER2- BC

In the global, double-blind, phase III study MONARCH 2 (NCT02107703), abemaciclib - a selective CDK4/6 inhibitor - plus fulvestrant significantly extended PFS and OS versus fulvestrant alone (mPFS 16.4 vs 9.3 months; mOS 46.7 vs 37.3 months) in patients with HR+/HER2- advanced BC [34, 35]. A pooled analysis of the endocrine therapy naïve (EN) participants of the MONARCH 2 study was presented at ESMO 2021 [36] .

In the EN cohort - consisting of EN patients with measurable disease excluded from the ITT population of

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MONARCH 2 (n=20) as well as additional participants enrolled under EN addendum (n=90) –, patients had a mean age of 54 years (range, 31 - 86), 43.6 % had an ECOG of 1 and 60.9 % were postmenopausal (natural or surgical). The participants received abemaciclib (200 mg or 150 mg twice daily [BD]) and fulvestrant (500 mg intramuscularly on day 1 and 15 of cycle 1, then day 1 of cycle 2 and subsequent cycles)). Most of the patients had ductal breast carcinoma (75.5 %), stage IV disease (69.1 %), at least three organs involved (68.2 %) and had ER+/PR+ (78.2 %) breast cancer at diagnosis.

After a median follow-up of 9.8 months, ORR assessed by investigator, which was the primary endpoint, was 59.1 %. One patient achieved a CR, 64 subjects experienced a PR, 20 patients had a stable disease (SD) lasting for at least six months, whereas one patient had progressive disease (PD). The clinical benefit rate (CBR) reached 77.3 % **(Figure 6)**, while PFS and DOR were not yet mature.

The safety profile was consistent with that previously reported in the MONARCH 2 main study. TEAEs of grade ≥ 3 occurred in 55.6 % of patients, the most common ones being neutropenia (23.1 %), diarrhea (13.9 %), and anemia (6.5 %).

These pooled data of the EN cohort confirmed the favorable ORR and the good safety profile previously reported for fulvestrant monotherapy in participants with a similar disease state.

SASCIA trial: a novel ADC in HER2- BC patients

Sacituzumab govitecan (SG), which has been approved by the U.S. FDA in April 2021 for the treatment of unresectable la/mTNBC patients with at least two prior therapies, is a novel Trop-2-directed antibody conjugated to a topoisomerase I inhibitor [37]. A prior phase I/II trial showed an ORR of 31 % and a CBR of 48 % for SG in heavily pretreated HR+/HER2- mBC patients [38].

At ESMO 2021, the study design of the ongoing phase III prospective, multi-center, randomized, open label, parallel group study, SASCIA trial (NCT04595565), was presented; this trial investigates SG in patients with HER2-negative BC with high relapse risk after standard neoadjuvant treatment [39]. Eligible patients (1,200 planned) have to be HER2- (centrally confirmed) and either HR+ (≥1 %) or HR- (<1 %) as assessed on tissues from post-neoadjuvant residuals of the breast or residual nodal invasion defined as follows: for HR- disease, any residual invasive disease > ypT1mi; for HR+ disease, a CPS+EG score ≥ 3, or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before the start of the neoadjuvant treatment. Subjects must have received a taxane-based neoadjuvant chemotherapy (NACT) for 16 weeks, including six weeks of a taxane. For patients with a progressive disease that occurred after at least six weeks of taxane-containing NACT, a total treatment period of less than 16 weeks is eligible. CPI therapy during NACT is allowed, while radiotherapy should be delivered before the begin of the study treatment. Patients are randomized (1:1) to receive either SG (10 mg/kg; days 1 and 8, Q3W, 8 cycles) or treatment of physician's choice (capecitabine, carboplatin, observation, endocrine-based therapy will be administered according to local guidelines). Primary study endpoint is invasive disease-free survival (iDFS); secondary endpoints include OS, safety, compliance, patient-reported outcome, quality of life, biomarker analysis and ctDNA dynamics.

The study, which is currently running in 32 German centers, is conducted in collaboration with the AGO-B Breast Study Group. Recruitment has started in December 2020 and will take an estimated 36 months. ■

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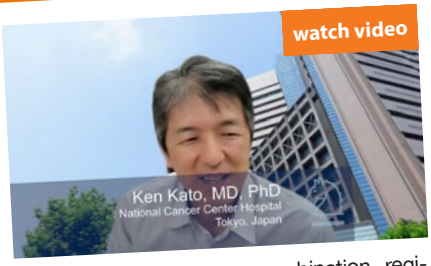
Expert interviews at ESMO 2021

Yelena Y. Janjigian talks about the practice-changing results obtained in the CheckMate 649 trial and how the proportion of patients with advanced gastric cancer and esophageal adenocarcinoma who receive multiple treatment lines rather than just one or two can be increased. Biomarker-targeted therapies, precision medicine approaches for advanced G/GEJ cancers, the significance of chemotherapy as well as the duration of maintenance therapy are discussed, too.

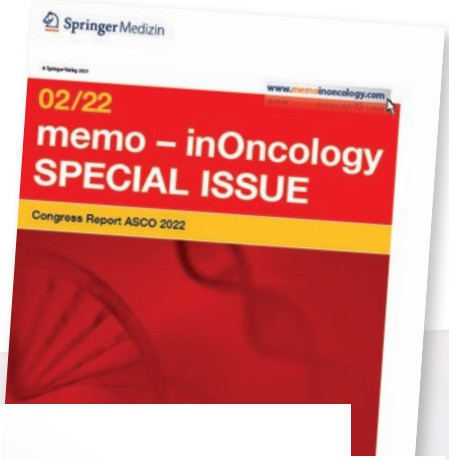


Ken Kato summarizes combination regimens currently investigated in the neoadjuvant treatment of patients with esophageal cancer and outlines how immunotherapy has changed the first-line treatment standards in patients with esophageal squamous-cell carcinoma and which further developments are expected for the first-and second-line setting in the future.

Ian Chau depicts the most interesting trial results in the field of esophageal cancer at the ESMO 2021 congress, gives an outlook on personalized approaches in the setting of esophageal squamous-cell carcinoma with regard to biomarkers for checkpoint inhibitors as well as potential further improvements of the prognosis of patients with esophageal cancer.

Chiara Cremolini gives an overview of strategies that might become available in the future to enhance the efficacy of immunotherapies in the setting of microsatellite-stable metastatic colorectal cancer, how to increase the proportion of patients with metastatic colorectal cancer who receive multiple treatment lines, the optimal continuum of care in 2021 in metastatic colorectal cancer and how to predict progressive disease.

Javier Cortés highlights the superiority of trastuzumab deruxtecan compared to trastuzumab emtansine in patients with HER2-positive metastatic breast cancer and the resulting future therapy algorithm, potential combinations in the management of patients with HER2-negative breast cancer and the clinical relevance of immunotherapy-based approaches in the treatment of triple-negative breast cancer.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2022 that will be held in June 2022. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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